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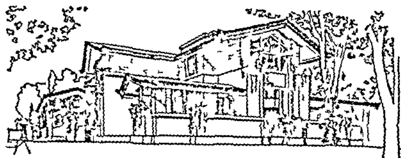
CAUSAL FACTORS IN
Cancer of the Lung

By

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ACKNOWLEDGMENTS

CREDIT for the substance of this Beaumont Lecture must be given to the hundreds of clinical and experimental investigators who for 500 years have sought to discover the etiology and pathogenesis of what is now known as bronchogenic carcinoma Reference will be made specifically to many published works and it is hoped that to some degree the usefulness of this monograph will depend upon its reasonably complete bibliographic documentation It has been found impossible to present a complete survey of the literature within the compass of one lecture even though liberal expansion has been permitted in the printed version Those writers who fail to find specific reference to their papers may be assured that the omission does not imply that their contributions were considered of lesser importance than those to which reference could be made

The author is responsible for the plan of organization and presentation He alone must bear the onus for excerpts from the literature which may seem too brief when encountered out of context and also for the many omissions The basic biologic philosophy of neoplasia presented here is by no means original It has developed gradually over many years and cannot be attributed to any one source It has been a fundamental concept in the teaching of the Department of Pathology of the University of Michigan for more than forty years

I owe personal acknowledgment to the professional members of my Staff who have volunteered to assume didactic and practical responsibilities which ordinarily are mine Without such relief this lecture could not have been prepared Dorothy E Seiferlein departmental executive

secretary and editorial assistant, has maintained th essential liaison with the Medical Library, has assisted n establishing the format, and has assumed personal respon sibility for the typescript

C V W

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CAUSAL FACTORS IN CANCER OF THE LUNG

I

INTRODUCTION

I WISH TO EXPRESS my deep appreciation of the invitation of the Wayne County Medical Society to give the Beaumont Lecture for 1955 When I read the list of distinguished teachers clinicians and investigators who have had this privilege in the past thirty four years my sense of appreciation deepened but at the same time I questioned my worthiness and my ability to approach the pattern of excellence which has been established by my predecessors

In a way my topic was chosen for me since the invitation was accompanied by a suggestion that I speak on cancer of the lung Obviously some limitation was required since only a restricted field could be explored and developed in one lecture That field was determined by those current circumstances which have created an intense interest in possible causal factors In bronchogenic carcinoma we have a malignant neoplasm of which the incidence has increased at an alarming rate within the lifetime of most of us The intrinsic qualities of human protoplasm cannot change that rapidly The evidence points to environmental factors I propose to explore with you the causes intrinsic and extrinsic proved and suspected of bronchogenic cancer In pursuing this purpose I shall draw upon medical history for clinical observations which have contributed to present knowledge This fusion of the old and the new is fully in keeping with the traditions of the Beaumont Lectures and tomorrow today will be history I shall endeavor to establish a general biologic

concept of causation in neoplasia and in particular of bronchogenic carcinoma, to assist in cultivating sound methods of evaluating causation, to present controversial matters impartially and to stress the fact that to the extent that an environmental factor can be established as the cause of any cancer to the same extent that cancer becomes a preventable disease

That productive investigator of the environmental causes of cancer W C Hueper, now at the National Cancer Institute has reminded me[1] that I wrote in 1929 [2]

> No other form of neoplastic disease is more intriguing from the standpoint of incidence than primary carcinoma of the lungs for within a generation it appears to have become one of the common forms of malignant disease instead of the rarity which it was believed to be at the beginning of the century

In the twenty six years since 1929 the gross incidence of pulmonary cancer has continued to increase and so has interest in the disease itself but more particularly in suspected causes The accumulated statistical information appears to implicate the smoking of tobacco as especially important This pleasant habit has long been under suspicion but in a rather detached way and at an academic level With the present emphasis this question has become a matter of personal concern to many millions There is also the possibility of a dislocating impact upon a segment of the national economy which extends from the plantation to the retail outlet It is natural that, under these stresses sound judgment yields to partisanship opponents and proponents use the same evidence to prove their respective views and lay editorial writers *instruct* the public

II

GENERAL CONSIDERATIONS

FOR ALL PRESENT PURPOSES cancer of the lung is bronchogenic carcinoma Primary sarcomas of the lung are rare The small round celled sarcoma of earlier days is properly identified as carcinoma with cells of a low level of differentiation It is true that there is an occasional example of a highly malignant neoplasm which has been variously designated as terminal bronchiolar carcinoma or alveolar cell cancer of the lung This highly malignant entity is represented in the Michigan necropsy material to an extent of less than one per cent It has certain structural resemblances to jagziekte a pulmonary disease of sheep in South Africa and Iceland This neoplasm is usually widely disseminated in both lungs in a manner which suggests aerogenous metastasis but which could be explained equally well if the causal agent is an air borne virus In my opinion this entity is an entirely different disease from bronchogenic carcinoma and it will not be included in further consideration of the causes of pulmonary cancer

Those new growths which are called bronchial adenomas likewise must be excluded from the general group of bronchogenic cancers This is done with some reluctance since bronchial "adenomas" may infiltrate locally and be found in adjacent lymph nodes However they differ so strikingly in age and sex incidence in potentiality for growth and in prognosis that only confusion would result if an attempt were made to include them in a discussion of etiologic factors for the highly malignant bronchogenic carcinomas

Bronchogenic carcinoma can arise in any portion of a lung but large bronchi are more commonly involved than the smaller branches Thus it comes about that there is a gradient of decreasing frequency from the hilar structures, as represented by the main stem bronchi and branches of the first order, toward the periphery of the lung This is reflected in the presenting signs and symptoms of the disease which are frequently those of a mediastinal tumor [3] cough pain in the chest, sputum, usually bloody or blood streaked at some time dyspnea cyanosis, venous and lymphatic engorgement of the upper part of the body laryngeal paralysis, hoarseness pupillary inequality, inequality of the radial pulses abdominal pain, dysphagia, and stertor In a second group the patient is led to seek medical advice because of general systemic effects such as loss of weight weakness chills and fever, anorexia, or nausea and vomiting A third group is established for those patients in whom there is early involvement of the pleura with pleural pain and a hemorrhagic pleural effusion Unfortunately, in some patients the presenting signs and symptoms may be provoked only by metastatic neoplasm and thus a fourth group must be established Many patients in this group will give evidence of a lesion of the central nervous system either encephalic or spinal The histologic examination of a tumor from the brain may give the first presumptive evidence of a bronchogenic carcinoma

Farber[4] found that 34 per cent of the patients included in his very large study group first sought medical attention because of symptoms which were due wholly or in part to metastatic lesions Knights[5] discovered that pulmonary cancer was the most common source of cerebral metastases in male patients (29 per cent) whereas mammary cancer took its place in female patients (47 per

cent) These figures were derived from 94 cases found in 6 500 necropsies at the Henry Ford Hospital Detroit

Because there is some suggestive information by no means clear cut as yet that there may be significant correlations between environmental causal factors and type of cell in bronchogenic carcinoma brief reference must be made to histologic features Regardless of reputed origin in large medium or small bronchi or even in mucosal glands three histologic types may be encountered These are designated as squamous celled gland celled and undifferentiated celled Although these terms might seem to be mutually exclusive no sharp lines can be drawn between groups Not only may great variation in cell type be found in different portions of the same neoplasm but there is a large group in any collected series in which neoplasm cells are in an intermediate level of differentiation Usually the squamous celled carcinomas predominate Farber's[4] figures recomputed on the basis of 849 necropsied patients of known cell type give 37 3 per cent squamous 28 0 per cent gland celled and 34 6 per cent with undifferentiated cells

Some years ago[4] I found that it facilitated presentation of the relationship between the various cell types of bronchogenic cancer if they are conceived as arranged in a Y shaped pattern (Figure 1) At the intersection of the stem of the Y and *its branches I locate* the neoplasms retaining the level of poorly differentiated "basal cells of normal bronchial mucosa Along the left hand inclined limb of the Y are distributed the carcinomas of gland celled type with the most fully differentiated columnar celled papillomatous mucin forming adenocarcinomas at the end of the line and less elaborately differentiated forms in descending pattern Those cancers with cells resembling the normal columnar bronchial epithelium

occupy about the position marked with x Similarly, at the extremity of the right hand limb are placed the heavily cornifying squamous celled carcinomas, followed by those with little or no keratohyalin and finally, by medullary carcinomas which have lost almost entirely the squamous celled character The stem of the Y receives the medullary carcinomas showing characteristics of

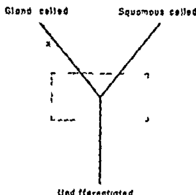


FIGURE 1 Scheme to show the mutual relationship of the cellular types of bronchogenic carcinoma

neither gland cells nor squamous cells These are sometimes referred to as oat seed carcinomas On the upper portion of the stem belong such carcinomas with plump cells and some trace of alveolar pattern Arranged progressively downward are the less well differentiated forms with diffusely infiltrating cancers which have very small spherical cells at the bottom of the figure

All investigators agree in classifying the carcinomas which would be placed near the extremities of the three branches but within the rectangular zone indicated by the broken line differences of opinion are inevitable Probably this is the chief reason for variance in statistical reports, but it may develop that certain study groups are differentially weighted in respect to age sex, or environ

mental risks It is because of this latter possibility that it has seemed necessary to restate this concept of the relationship of cell types in bronchogenic carcinoma There is even now some evidence that the proportion of squamous celled carcinomas is increased under the influence of particular environmental factors and that the incidence of gland celled carcinomas more nearly represents a basic state not significantly altered by the presently suspected extrinsic factors

INCIDENCE

General Incidence The importance of bronchogenic carcinoma in current medical experience scarcely needs

TABLE I
MALES (ALL AGES)
ANNUAL MORTALITY FROM CANCER OF THE LUNG
PER MILLION LIVING

United States			*New York State*		
1930	1945	Increase	1931-33	1948 50	Increase
31	132	*Per Cent* 326	47	228	*Per Cent* 385

Age distribution adjusted to that for New York in 1940 (After Levin[4])

emphasis For documentation of the picture as of recent years such statistical analyses as that of Dorn[1] are available He stated in 1953 that 8 1 per cent of all deaths from malignant neoplasms can now be attributed to cancer of the lung and bronchus This is in reference to all ages and both sexes The impact of this statement is felt all the more forcibly when the concentration of bronchogenic cancer in males of late middle life is realized For the United States as of 1945 Levin[4] stated that the annual mortality from cancer of the lung was 568 per million living for males fifty five to sixty four years of age and 599 for those sixty five to seventy years of age

A striking feature has been the apparent continuous increase for the past fifty years This was evident in 1929 when I[2] reviewed earlier literature giving the incidence as found in over 600,000 necropsies The results appeared to show a five fold increase when the period 1872 to 1898 was compared with that of 1916 to 1924 For more recent periods we can abstract the material of Table I from a

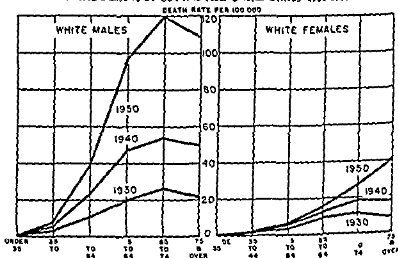


FIGURE 2 Mortality from cancer of the respiratory system Reproduced by permission from the *Statistical Bulletin of the Metropolitan Life Insurance Company* [9]

detailed arrangement by Levin [8] For white persons the change between 1930 and 1950 is presented graphically in Figure 2 which shows an almost six fold increase for white males of the age group sixty five to seventy four in that period [9] Thus the apparent rising incidence noted in earlier years is not only continuing but has been accelerated

There has always been serious questioning as to whether this increase is due to purely relative factors or

to an actual greater propensity, whether natural or induced on the part of human tissue to develop this form of cancer The two views are sometimes expressed by contrasting "true" with "relative" incidence This is an unfortunate designation for no one can deny that there is a

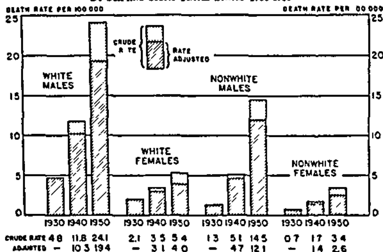


Figure 3 Mortality from cancer of the respiratory system The stippled portions of the bars indicate the portion of the mortality which can be attributed to the increased age of the population Reproduced by permission from the *Statistical Bulletin of the Metropolitan Life Insurance Company* [9]

true increase "Real" and "relative" are somewhat better adjectives for designating the difference However the mind has been reluctant to admit that cancer may be due to changing responses between the body and its environment and wherever possible has sought other explanations for the increase in bronchogenic carcinoma Such reasons are not hard to find

1 To what degree is the increase due to the changing distribution of our population in respect to age? More persons are living in the age period in which broncho genic carcinoma occurs If there are significant environ mental causes, it may be that this is simply another way of stating that more people are exposed, and exposed longer to provocative agents That age distribution can

TABLE II
DISTRIBUTION OF 313 PULMONARY CARCINOMAS IN 14 000 NECROPSIES (UNIVERSITY OF MICHIGAN)
1895 1954

Necropsies by Thousands	*Males*	*Females*	*Total*
0 1000	2		2
1001 2000	8		8
2001 3000	9	1	10
3001 4000	10	4	14
4001 5000	16	2	18
5001 6000	17	4	21
6001 7000	18	4	22
7001 8000	17	5	22
8001 9000	21	3	24
9001 10000	21	5	26
10001 11000	30	1	31
11001 12000	34	5	39
12001 13000	31	3	34
13001 14000	37	5	42
Totals	271	42	313

account for approximately one fifth of the increase be tween 1930 and 1950 is shown in Figure 3 The stippled area at the summit of each bar indicates the reduction in the crude rate which would have been experienced if the population had remained with the same distribution in respect to age sex and color in 1940 and 1950 as was true in 1930 Of the three variables only age proves to be of great importance in influencing the change *in inci dence*

2 It has been suggested that the increase is due to more

accurate certification of the causes of death resulting from the use of such diagnostic methods as roentgenoscopy bronchoscopy tissue biopsy exploratory thoracotomy, and cytologic study Since these measures have been introduced successively and employed with constantly increasing effectiveness, a gradual and not an abrupt increase in the apparent incidence might be expected The increase has followed such a pattern with a fairly smooth gradient It is impossible to assess the effect of better diagnoses with any degree of accuracy, and it must be remembered that improved diagnostic methods will not necessarily yield higher figures for incidence Some of the errors would have been in the opposite direction of certifying deaths as due to pulmonary cancer when such was not the case Moreover the early values for incidence were based on necropsy experience and the continuity of methods and personnel in many institutes of Pathology has been such that there is no possibility that a significant number of cases of bronchogenic cancer were missed in earlier years In Table II the distribution of bronchogenic carcinoma in 14 000 necropsies at the University of Michigan is shown by thousands of necropsies and the same material is presented graphically in Figure 1 Divided into numerical halves the first 7 000 included 95 cases of bronchogenic carcinoma or 30 per cent of the total number Divided chronologically into half periods the necropsies (two) on patients with bronchogenic carcinoma in the first twenty nine years were too few to be statistically significant due in part to the fewer necropsies of that period They amounted to 0 23 per cent For the second half period 2 37 per cent of the necropsies have been upon patients with bronchogenic carcinoma Because the older material is at hand for study and has been reviewed from time to time there is no possibility that

bronchogenic carcinoma was missed to a significant ex tent in the earlier years

3 A third basis for an apparent rather than a real in crease in bronchogenic cancer concerns a complex of

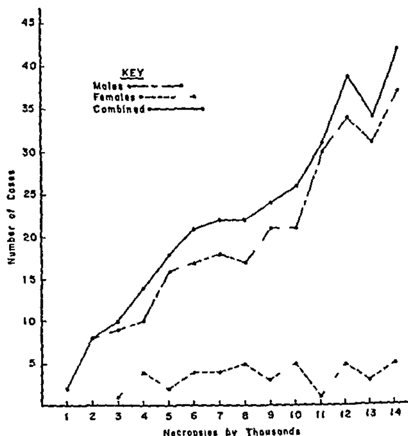


FIGURE 4 Distribution of 313 cases of bronchogenic carcinoma in 14 000 necropsies in the University of Michigan series

imponderable considerations such as growth of lay knowl edge and interest in cancer, lay insistence on securing better diagnostic aid more extensive referral of patients with diagnostic problems, and greater professional inter est and awareness in respect to bronchogenic carcinoma

Clearly, these considerations overlap the improved diagnostic procedures discussed in the preceding paragraph and like them can operate in both a positive and a negative direction Probably some patients are now correctly diagnosed as having cancer of the lung who previously would have been certified as dying of chronic tuberculosis chronic pneumonitis asthma, or even the totally unacceptable general debility

In summary practically all who have investigated the problem of changing incidence of cancer of the lung agree that some of the increase is "apparent" and depends chiefly on increasing longevity but that there is also a real increase which provides the immediate incentive for the further exploration of causal factors

Age Incidence As is shown by the current study (Figure 2) from the Metropolitan Life Insurance Company [9] the peak of mortality from pulmonary cancer for white males in the United States occurs in the decade of sixty five to seventy four years of age Incidence increases rapidly after age forty and the rate of increase (indicated by steepness of the curve) is greatest for the interval between fifty and sixty Similar results have been found in most countries where similar studies have been made Beyond age seventy four mortality continues to show a very marked increase over the experience for that age group in earlier periods but for the contemporary population the rate of change is reversed and the curve declines Yet it remains truly alarming that for the group seventy five years old and older the mortality from cancer of the lung was five and one-half times greater in 1950 than in 1930

The down turn in the mortality curve for white males after age seventy four has been evident in each of the periods indicated in Figure 2 A similar reduction in mortality in advanced years has been observed in most geo-

graphic areas, but not always beginning at exactly the same age The significance of this decline is as yet un known When the answer is determined it may supply the key for confirming the importance of environmental factors which are now under suspicion Among possible explanations are the following

1 The aged group may receive less sympathetic and skillful diagnostic attention in view of the improbability that curative treatment can be applied regardless of the diagnosis It is surprising how often it is forgotten that *the person who has lived beyond the life expectancy of his* birth, still has the life expectancy of the age group of which he is now a member

2 The aged group may contain a higher proportion of those whose cells are intrinsically less easily provoked, by environmental factors to that proliferative activity which constitutes cancer

3 It may be that in the older group are those who have not been exposed either in intensity or duration or in both intensity and duration to one or more provocative factors which have come more recently into human en vironment This was apparently the thought of Korteweg[10] when he predicted that the greater part of the future in crease in mortality from cancer of the lung will concern persons more than sixty years of age

In presenting these possibilities it has been necessary to anticipate considerations which are developed more fully in the section on Etiologic Factors in Neoplasia Intrinsic and Extrinsic

Only for white females for the year 1950 do we find an ascending mortality curve after age seventy four Ten years before this had been anticipated by a constant level This is probably significant in respect to a current change in incidence The tables of Kennaway and Waller[11] show

that for England and Wales since 1920 the highest mortality for cancer of the lung bronchus and pleura in females has occurred about ten years later than in males

Sex Incidence For the lung as for the lower lip, mouth and esophagus there is marked inequality in the incidence of cancer in respect to sex As determined by mortality statistics, there has been a progressive widening of the gap between men and women Thirty years ago the ratio of deaths from this condition for men and for women

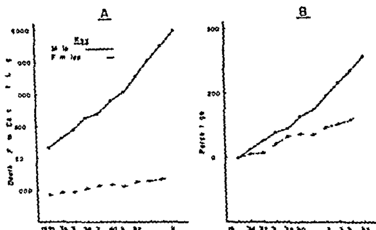


FIGURE 5 Graphic comparison between (A) total mortality for males and females and (B) the annual percentage increase for each sex with 1935 considered unity Vital statistics of bronchogenic carcinoma in England and Wales [13] (Redrawn by permission from Kennaway and Kennaway *Brit J Cancer 1* 260-298 1947)

was about 3:1 Dorn[7] has stated recently that for the United States the ratio is now about 5:1 Considerable variance from this ratio has been noted in other countries in comparing rural and urban populations and in the more or less peculiar experience of particular hospitals In the University of Michigan necropsy series (1895-1934)

of 313 cases in 14,000 necropsies the ratio as to sex has been 6 5 1 Farber[4] referred to a 9 1 ratio for his study group of 1,070 cases

It is necessary to keep in mind the difference between the comparative mortality of the sexes and the comparative change in incidence Even with the same effective rate of increase for females as for males the spread between the sexes as shown by figures for gross morbidity or mortality would continue to widen because of the larger base for males to which the rate is applied Disregard of this obvious consideration leads to a distorted concept of the relationship between sex and bronchogenic carcinoma This was explained by the Kennaways in 1936[12] and again in 1947[13] and Figure 5 is redrawn from material which they presented in the latter year The graph in the left half of the figure is based on the actual number of deaths from cancer of the lungs in England and Wales for the period 1935 to 1945 The same data are presented on the right but deaths per annum for each sex are indicated as a percentage of those of 1935 considered as 100 The changes in rate of increase as applied to males and to females of successive age groups may aid in the identification of significant environmental factors and in determining the required period (latent period) for the origin and development of a neoplasm Such analyses should prove increasingly helpful

The sex of the patient influences the cellular type of bronchogenic carcinoma A recent study by Steele[14] gives the distribution in a group of 201 cases Of the patients with squamous celled carcinoma, 97 per cent were men of those with undifferentiated carcinoma 88 per cent were men, of those with adenocarcinoma, 65 per cent were men This relationship may be due to intrinsic differences between the sexes which are apart from environmental

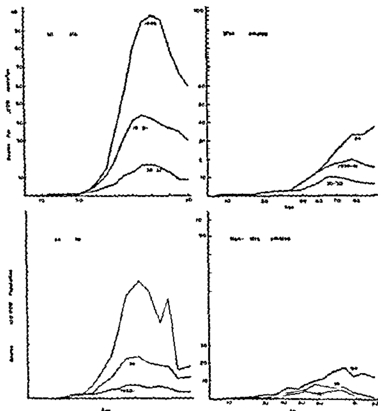


Figure 6 Mortality rates for cancer of lung and bronchus by age color and sex United States 1930 1932 1939 1941 and 1949 [7] (Redrawn by permission from Dorn *Acta Unio Internationalis Contra Cancrum* 9 532-561 1953)

factors to exposure to different environmental factors to exposure to the same environmental factors to different degrees or to different tissue response to the same environmental factors There is increasing evidence that with known environmental factors squamous-celled carcinoma is more often the result Therefore in considering

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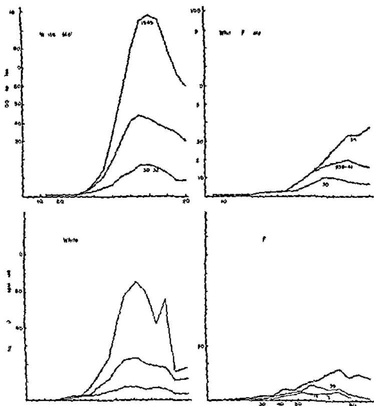


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factors to exposure to different environmental factors to exposure to the same environmental factors to different degrees or to different tissue response to the same environmental factors There is increasing evidence that with known environmental factors squamous-celled carcinoma is more often the result Therefore in considering

the causes of bronchogenic carcinoma, *maleness* must be included There may be fundamental differences in the male which make him more vulnerable to the influence of his environment Sex hormones can produce both morphologic and physiologic changes in squamous mucosa

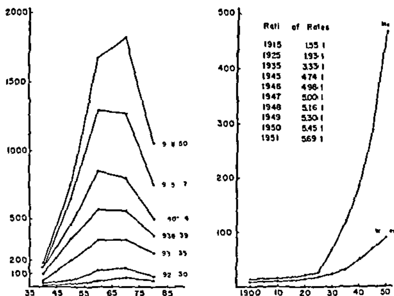


Figure 7 At the left mortality from lung cancer among men at different ages Britain 1911 1950 At the right death rates from lung cancer in England and Wales as to sex and ratio between sexes 1900 1950[16] (Redrawn by permission from Doll *Brit M J* 2 521 527 585 590 1953)

Moreover, Moore and Barr[15] have shown that even in the somatic cells there are recognizable differences in the nuclear apparatus of the sexes Perhaps *maleness* is only a conditioning or synergistic factor but its importance is *increasingly evident*

As Figure 6 four graphs from Dorn[7] are redrawn to the same scale Together they give mortality rates from cancer of the lung in the United States over a span of twenty

years distributed by age, color, and sex When all of the facts of causation are fully known the striking differences in the resulting twelve curves will find explanation

The curves for white males in Britain (Doll[16]) have, in general a similar form to those for the same group in the United States, and are shown in Figure 7 The accelerated

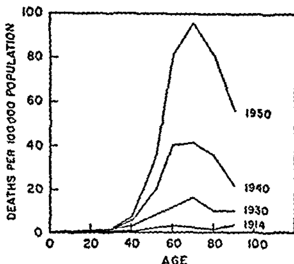


FIGURE 8 Death rates from cancer of the lung by age white males United States 1914 1930 1940 and 1950[17] (Reproduced by permission from Cutler and Loveland *J Nat Cancer Inst* 15 201 211 1954)

increase of the preceding decade is strikingly evident Increasing incidence in females, also, is shown in the right half of this figure which is based on mortality returns from England and Wales but the rate of acceleration is lower so that the proportion of male female deaths rose from 1 55 1 in 1915 to 5 69 1 in 1951

The Risk of Developing Cancer of the Lung The probability of developing cancer of the lung between

specified ages depends upon the incidence rates of cancer of the lung at the specified and intervening ages and the probability of dying from any cause at the different ages Cutler and Loveland[17] have determined this probability for white males by utilizing the United States life tables with a method of cohort analysis which takes into account both the increasing incidence of cancer of the lung on the one hand and the increasing life expectancy of the mem-

TABLE III
EXPECTED NUMBER OF CASES OF LUNG CANCER IN A COHORT OF 100 000 WHITE MALES BORN IN 1910

For Age interval	*Number Alive at Beginning of Interval*	*Person Years of Life During Interval*	*Expected Number of New Cases in Interval*	*Cumulative Cases in This and All Subsequent Intervals*
30-40	93 572	925 732	33	3 990
40-50	91 295	889 491	218	3 957
50 60	85 798	803 610	785	3 739
60 70	73 501	635,533	1,502	2 954
70 80	52 178	385 688	1 452	1 452

Reproduced by permission from Cutler and Loveland [17] *J Nat Cancer Inst* *15* 201 211 1954

bers of each successive cohort on the other Death rates from cancer of the lung by age of white males of the United States are shown as of 1914 1930, 1940 and 1950 in Figure 8 These authors made use of the cancer surveys conducted in 1947 by the National Cancer Institute[18] in ten urban areas for additional information on morbidity and mortality from cancer of the lung Naturally the values will differ for each year of birth but our immediate interest is with those born in 1910 and in the decade before and after that year For this group Cutler and Loveland developed a table of probabilities, which I have abridged as Table III It may be noted that 3 957 cases of cancer of the lung may be expected to develop by age

eighty among 91,295 white males of this cohort alive at age forty From this analysis of past experience and for ward projection the authors estimated that of every 1 000 white males born in 1910 and still living in 1950 eleven may be expected to develop cancer of the lung by age sixty, twenty seven by age seventy and forty three by age eighty This projection gives recognition to evidence that while the incidence of cancer of the lung is still increasing the rate of increase is progressively decreasing Therefore the rates as forecast by Cutler and Loveland are not as high as have been computed by some others

For those not trained in biostatistics such data may seem complex and difficult of interpretation What they mean for each of us or for the male infant born in 1954 is not easily appreciated but there is crystal clarity in the following sentences which I quote from M L Levin[19] 1954

> In less than a decade the chance of developing lung cancer at some time during life has more than doubled among males in New York State Two per cent of all males may be expected to develop lung cancer at present rates of incidence

Etiologic Factors in Neoplasia Intrinsic and Extrinsic

If causation be considered in its broadest aspects with due regard to both causal genesis and formal genesis it will be found that disease is never the result of a single factor Two causes or groups of causes must be considered One of these has origin in the germ plasm of the individ ual the other is brought to bear upon the inherent pattern of living organism from outside the realm of chromosomes and genes The source of this latter cause may be found either within the body or in the extracorporal environ

ment, but it is quite apart from the germ plasm Consideration of this relationship leads to the conclusion that such antithetical pairs of words as internal and external, endogenous and exogenous, and even constitutional and environmental fail to designate adequately the major groups of factors With definition, *intrinsic* and *extrinsic* meet this need with complete satisfaction

Intrinsic causes of disease lie within the germ plasm All other causes of disease are *extrinsic* It can usually be shown that if the ultimate cause (causal genesis) of a disease is intrinsic or extrinsic its mode of development and manner of expression will be conditioned by extrinsic or intrinsic factors (formal genesis), respectively For instance, true hemophilia is entirely hereditary and therefore intrinsic as to its actual cause but the expression of hemophilia in each of its victims will depend upon the vascular channels which are opened by extrinsic factors Conversely, *Treponema pallidum* is entirely an extrinsic factor There is no hereditary lues, although the phrase is often carelessly used as a synonym for congenital syphilis Yet the disease produced by this extrinsic factor varies from patient to patient depending upon age, sex and race because intrinsic factors are conditioning the body's response to the causal agent For each disease entity the proportion of these causal ingredients varies There is no reason for believing that neoplasia is unlike other diseases in having such dual elements in causation [20] The interplay of intrinsic and extrinsic factors is indicated schematically in Figure 9

For some neoplasms the intrinsic factor is very important This has long been recognized for carcinoma of the large bowel developing upon the substratum of familial polyposis[21], and the extraordinary concentration of retinoblastoma in certain families [2] far exceeds the most remote

possibility under free chance distribution There is substantial evidence that for such new growths somatic variations are inherited and that it is upon these structural deviations from the normal that cancer arises This thesis need not be developed here for there are other malignant neoplasms—and fortunately bronchogenic carcinoma is one of them—in respect to which a specific intrinsic factor has never been proved to be important

It is obvious that basic intrinsic factors are concerned

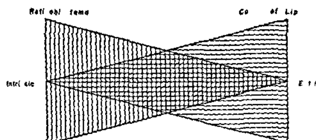


FIGURE 9 Schematic representation of the relationship between intrinsic and extrinsic causal factors in neoplasia

with the development of all neoplasms as they are with normal growth for behind every neoplasm is the intrinsic urge toward cell division and growth Such factors must be accepted as part of the total picture of the causation of cancer These are not the specific intrinsic factors which give certain neoplasms a hereditary pattern and which I contrast with extrinsic factors Although common to both normal and neoplastic growth the basic intrinsic urge must operate with different degrees of intensity under varying conditions and in different subjects To this biologic substratum are to be added specific intrinsic factors if any and whatever extrinsic factors may be operative

I have just stated that it is fortunate that bronchogenic

carcinoma gives no evidence of any potent specific intrinsic factor If there is a hereditary pattern for this neoplasm, it is below the horizon This makes it all the more probable that there are significant extrinsic factors Once an extrinsic factor is established, the way has been opened for attempting prevention In the opening paragraph of his article on the socio-economic distribution of gastric carcinoma, E M Cohart [3] has written

> since the time of Percivall Pott almost without exception our all too-scant accomplishments in the prevention of cancer have grown out of epidemiological observation

It is my purpose to review, in that which follows, certain of the historical aspects of the search for extrinsic factors causing cancer, with particular reference to bronchogenic carcinoma I will show that diverse threads of evidence, beginning more than 500 years ago and weaving an intricate design, are now giving promise of revealing enough of the true pattern to suggest that to an as yet undeterminable degree bronchogenic carcinoma is a preventable disease

III

THE FIRST THEME BERGKRANKHEIT IN THE ERZGEBIRGE—SCHNEEBERG AND JOACHIMSTHAL (JÁCHYMOV*)

CARCINOMA OF THE LUNG as an endemic occupational disease in the miners in the Erzgebirge (Ore Moun tains) of Saxony and Bohemia is as well known to students of bronchogenic cancer as is the work of Beaumont to physiologists internists and medical historians Unlike the achievements of Beaumont which in the words of your lecturer of 1953[24] were the inception of the modern physiological approach to clinical problems of the gastro intestinal tract intensive investigation of this occupa tional disease has not yet led to results in keeping with the effort expended

The miners of Schneeberg in Saxony and of Joachims thal (now Jáchymov) in Bohemia have been for at least 500 years the victims of a chronic pulmonary disease now known to be carcinoma From references in the literature beginning early in the sixteenth century from parish and other registries and from extensive investigations con ducted in the first quarter of the present century, it has been established that this particular Bergkrankheit was the cause of death in from 44 to 75 per cent of the active and pensioned miners The clinical picture of the dis ease unvaried through the centuries was marked by cough mucoid mucopurulent or bloody sputum increas ing dyspnea loss of strength and weight increased sweat

* Joachimsthal = Joachimstal = Jáchymov

GEORGII AGRICOLAE

DE RE METALLICA LIBRI XII. QVI-
bus Officia, Instrumenta, Machinæ, ac omnia deniq; ad Metallicam spectantia, non modo luculentissimè describuntur, sed & per effigies suis locis insertas, adiunctis Latinis, Germanicisq; appellationibus ita ob oculos ponuntur, ut clarius tradi non possint.

E I V S D E M

DE ANIMANTIBVS SVBTERRANEIS Liber ab Autore recognitus, cum Indicibus diversis, quicquid in opere tractatum est, pulchre demonstrantibus



BASILEAE M. D. LVI.

Cum Priuilegio Imperatoris in annos v.
& Galliarum Regis ad Sexennium.

FIGURE 10 Title page of *De Re Metallica* Libri XII by George Agricola 1556

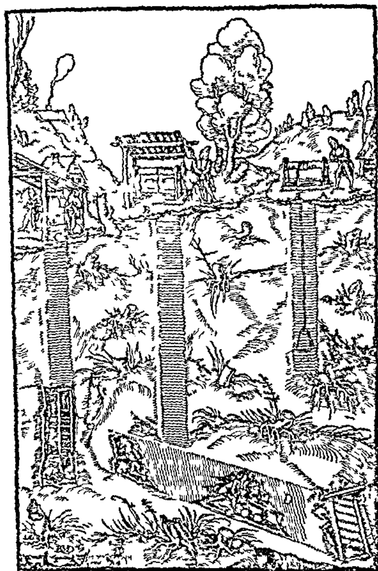


FIGURE 11 This illustration from *De Re Metallica* gives an indication of the long ladders which the miners had to employ in going to and from work.

ing boring pain in the chest or back, and inevitably, death after a varying period of incapacity Miners thus afflicted were said to be "bergfertig" that is so enfeebled in health by mining as to be unable to continue working

Historical references to this unique occupational disease emerge from the Middle Ages Pirchan and Šikl[25] wrote that it was mentioned by Agricola in 1500 If so the renowned "father of mineralogy" was a very precocious child for in that year he would have attained the ripe age of six years "[6] However only the too well rounded date was in error Who of that period would have been better qualified to record the miners diseases of Joachimsthal? About 1527 Agricola born Bauer was made town physician of this flourishing mining village from the silver coinage of which (Joachimsthaler) our American word "dollar" was derived Already the author of scholarly books Agricola continued his studies of mines and mining His principal work *De Re Metallica* long remained the standard technical treatise on mining and smelting I quote him from the translation by the Honorable Herbert Clark Hoover and Lou Henry Hoover[26] as follows

> Of the illnesses some affect the joints others attack the lungs some the eyes and finally some are fatal to men Where water in shafts is abundant and very cold it frequently injures the limbs On the other hand some mines are so dry that they are entirely devoid of water, and this dryness causes the workmen even greater harm for the dust which is stirred and beaten up by digging penetrates into the windpipe and lungs and produces difficulty in breathing and the disease which the Greeks call ασθμα If the dust has corrosive qualities it eats away the lungs and implants consumption in the body, hence in the mines of the Carpathian Mountains women are found who have married seven husbands all of whom

this terrible consumption has carried off to a premature death

Two hundred and fifteen years after the publication of Agricola's treatise Scheffler[27] showed that this fatal ail



FIGURE 12 This illustration from *De Re Metallica* shows an early method by which the hard rock of the tunnel wall was cracked by building fires against it

ment could not be pneumonia or peripneumonia because it lasted too long and could not be asthma montanum because asthma did not produce destructive lesions in the lung and after another 100 years Harting and Hesse[28] established in 1879 that the endemic occupational dis

ease of Schneeberg was primary cancer of the lung and that about 75 per cent of the deaths of miners were from this cause From observations made in the course of twenty necropsies, they concluded that the cancer was a lymphosarcoma, or, rarely, an endothelial carcinoma (The interpretation of a poorly differentiated round celled carcinoma as lymphosarcoma is an easily under stood error, and one from which we are not entirely free today) Arsenic especially in combination with nickel and cobalt, was considered by Harting and Hesse to be the directly injurious, causative agent They were fully aware that miners cancer of the lung developed only after many years of labor They wrote that at the earliest, it appeared after twenty years usually after a longer period, and sometimes after as long as fifty years All subsequent investigators have recognized a long latent period although the average work period before the devel opment of the disease was found to be somewhat shorter than was stated by Harting and Hesse This feature was far more important than would at first appear The in escapable corollary was and is, that the results of modifi cation of environmental conditions cannot be known with certainty until at least two decades have passed In fact it seems not unreasonable to predict that for certain forms of cancer as related to particular extrinsic factors, it may be necessary to await the vital statistics of another gen eration before the results of preventive measures will be known beyond reasonable doubt

It would be inconsistent with the limits which must be placed upon other phases of this discussion to review the many scientific contributions dealing with the miners cancer of Schneeberg and Joachimsthal but certain de velopments must receive further attention

Harting [8] like Agricola was a local physician in these

mining communities With Hesse he explored every phase of the mode of living and working of the miners from the rancid Galician butter which must be used during a portion of the year to the amount of oil which each miner burned in his lamp while underground He was interested in the oil as a source of carbon dioxide As will be developed later had he possessed our present information he would have been more concerned with the oil as a source of the intermediate products of incomplete combustion In their first illustrative clinical report which concerned a thirty six year old miner who had been employed for twenty and one half years it is evident that inquiry was made as to his smoking habits for he is quoted in translation "I have smoked tobacco but not to excess in the last year little and then only at home This was in 1878

During the first fifty years of medical and physicochemical investigation many environmental factors were suggested as of causal significance for Schneeberg cancer The miners were compelled to descend and ascend ladders for considerable distances sometimes as much as 1 000 feet The working shifts were long and the labor heavy In the harder rock where drilling was necessary fine stone dust was produced in quantity Arsenic present in a content of 0 5 per cent in some of the rock dust was suspect as were also the abundant moulds growing luxuriantly on and in the timbers of damp portions of the workings Carbon dioxide not only from the miners oil lamps but also from fires built against the face of the rock and smoke and other fumes from these sources and from the use of blasting powder and dynamite were given consideration This by no means exhausts the list of hazards which were explored

Margarete Uhlig[29] in 1921 and while still a candidate

for her Doctorate in Medicine, produced an admirable study of cancer of the lungs in the Schneeberg miners Like Agricola and Harting she wrote from on the scene experience The opening sentence of her report in the Virchow *Archiv* can be translated In my native town, the old village of Schneeberg in the Ore Mountains, the expression 'bergfertig often is heard After discussing the various causal factors proposed by her predecessors, she wrote that she had seen a published article "by a layman, to be sure in which the Schneeberg lung cancer was explained as an occupational disease of mines in which the rock contained radium and in which the air contained radium emanations Both of these conditions were met to varying degrees in the Schneeberg mines but even more so at Joachimsthal In fact it was from Joachimsthal that the Austrian government had obtained the ton or so of residual material (after the recovery of uranium from pitchblende) from which the Curies in 1898 isolated radium chloride It was natural therefore for Margarete Uhlig whose reference to the unproved causative action of radium and radium emanation in respect to cancer of the lung is the first that I have found in medical literature to turn to Joachimsthal for further evidence If this was the explanation of the miners cancer of Schneeberg she reasoned the incidence of the disease should be greater in Joachimsthal where the rocks and ore possessed greater radioactivity Her inquiry directed to Langhans brought the reply that at Joachimsthal there were no proved cases of cancer of the lungs known to him It subsequently developed that only the lack of necropsies had prevented recognition of the fact that pulmonary cancer was an occupational disease in Joachimsthal as well as in Schneeberg Somewhat later when this truth was known Peller[30] computed that the liability of the miners of Joachimsthal to cancer of the lungs was twenty eight times

greater than that of males of corresponding age in Vienna

Arnstein[31] had shown in 1913 that the cancer of one Schneeberg miner was clearly squamous celled Beginning in 1921 thorough clinical roentgenologic and pathologic studies of lung cancer in the Schneeberg miners were carried on by Thiele Rostoski Saupe and Schmorl[5, 35] in the course of which it was established that all of the neoplasms encountered were carcinomas that pulmonary cancer was still endemic in this group and that it occurred only in those who worked underground or were in intimate contact with the products of the mines

As to Joachimsthal the first case of cancer of the lung to be recognized on the Bohemian side of the Erz Mountains was observed by Pirchan in 1926 according to Pirchan and Šikl[25] who mentioned it in their review This occurred in a worker in the radium factory In 1929 Lowy[36] referred to the many deaths which had been observed in miners and radium factory workers between thirty and forty years of age described the signs and symptoms and proved that two patients had cancer of the lung, in one case by bronchoscopic examination, and in the other by necropsy With more frequent necropsies it was established by Šikl[37, 38] and his associates that cancer of the lung was highly prevalent and that the time spent in the mines by those who developed cancer ranged from thirteen to twenty three years Whereas Schmorl[5] had emphasized pneumoconiosis as of probable prime importance at Schneeberg no notable degree of silicosis or pneumoconiosis was found at Jáchymov By Šikl radium emanation, found in the air of some of the pits in a concentration up to 50 Mache units was considered the more important cause of cancer of the lung

As has been stated several environmental factors which attracted early attention as possible causes of cancer of the lung at Schneeberg and Joachimsthal can be elim

inated for one or both of two reasons (a) they were not restricted in their application to those of the local population who went underground or were in close association with the products of the mines above ground, (b) they were not peculiar to mines and mining in this district, as compared to other geographic areas After these eliminations there remained four possible causes each of which will be discussed in its appropriate relationship to other than the local problem These are

1 Pneumoconiosis including chalicosis in general, and more particularly, silicosis
2 Compounds of cobalt and nickel
3 Arsenic
4 Radioactivity

No one has suggested that the miners of the Erzgebirge used more tobacco than their fellow townsmen who did not go underground Moreover Agricola was born only two years after the discovery of America and the first use of tobacco in Europe is said to have been in England in 1586

What is the situation in Schneeberg and Joachimsthal today? Perhaps some of the answers are known by appropriate governmental agencies but they are not to be found in medical literature for the Ore Mountains are well behind the iron curtain" The flow of information ceased about 1939 and has not been reopened This is all the more understandable in view of the present necessity for the production of uranium Successively, this region has been exploited for silver for nickel cobalt bismuth and arsenic for radium and now for uranium A generation has passed since corrective measures were being introduced to mitigate some of the hazards Hoists were provided to make climbing the long ladders unnecessary hours of labor were to be reduced and more

mechanical equipment provided more effective forced ventilation was recommended to reduce the atmospheric content of both rock dust and radium emanation respirators were provided and wet drilling encouraged in the dusty areas Let us hope that in years to come international tensions will be relaxed to the degree that we may learn whether the incidence of cancer of the lung in Schneeberg Jachymov and neighboring mining areas has been lowered by such measures, and thus we may gain insight in respect to causation Or will it be revealed that in the competitive struggle for uranium hundreds or thousands of new workers have been exposed perhaps unwillingly to environmental hazards which are almost inexorable causes of cancer of the lungs?

Fortified with basic information in respect to Schneeberg cancer it is now possible to proceed to consideration of selected extrinsic factors which were postulated for Bergkrankheit It has been suggested that there was an intrinsic (hereditary) factor operating in Schneeberg and Joachimsthal through many generations of intermarriage as a result of social isolation There is no evidence to support this view

CHALICOSIS, WITH SPECIAL REFERENCE TO SILICOSIS

By the early investigators of cancer of the lung in the Schneeberg miners stone dust was considered important but usually for other reasons than its content of silica Šikl[33] found that an association of carcinoma of the lung with silicosis was exceptional in the necropsies upon miners at Joachimsthal He was convinced that no essential role could be attributed to silicosis However many authors from various geographic areas have been impressed by the coincidence of silicosis and pulmonary cancer in a single case or a small group of cases It must be remembered that when two conditions are each rela

tively common, chance distribution will lead to their simultaneous occurrence to an extent which is predictable if the incidence of each is known

The comparative study of pulmonary cancer in relation to silicosis by Klotz[39] often is cited as in support of a causative relation, although Klotz was very guarded in his own conclusions He found an incidence of lung cancer of 8 per cent among 50 silicotic patients as compared with an incidence of 1 17 per cent in 4,500 unselected necropsies Such a comparison is statistically unsound The four examples of combined silicosis and carcinoma were in males forty five to fifty four years of age The control group should have matched them in sex and age instead of being *unselected* *Quite apart from this comparative* inadequacy the occurrence of four cases of pulmonary cancer in a group of fifty middle aged males is of dubious statistical significance in view of the general incidence of the disease during the period when these cases were being collected

Kennaway and Kennaway,[12] after tabulating occupational hazards from the death certificates of England and Wales for the period 1920 to 1932 concluded that some excess of cancers of the respiratory tract was found in association with certain dusty occupations but that, in general, activities leading to silicosis played no important role in the production of cancer

Extensive studies of South African gold miners, based on necropsies in Johannesburg have been interpreted as demonstrating that silicosis was neither a causal nor predisposing factor for pulmonary cancer Table IV arranged by Hueper[1] from *Reports of the Miner s Phthisis Medical Bureau of South Africa*, gives the percentage incidence and coincidence of silicosis and pulmonary cancer in 3 215 European males for 1932 and 4 510 for 1935

Vorwald and Karr[40] reviewed the literature compiled their own observations, and exposed 3 338 animals to various mineral dusts for long periods They reached the conclusion that rock dusts in general and silica cannot be considered etiologic factors in the development of pul monary cancer Also Schulte[41] found among the miners of the Ruhr that combined roentgenologic and necropsy *studies established a complete dissociation between sili* cosis and cancer of the lung

TABLE IV
COINCIDENCE OF PULMONARY CANCER AND SILICOSIS IN SOUTH AFRICA

	European Non miners	*European Miners Without Silicosis*	*European Miners With Silicosis*
1932			
Necropsies	1023	1109	1083
Lung cancer per cent	0 58	054	0 37
1935			
Necropsies	1393	1679	1438
Lung cancer per cent	0 93	0 71	0 70

From Reports of the Miner s Phthisis Medical Bureau of South Africa (Cited by Hueper[5])

There is a corollary to the apparently well established fact that silicosis has no etiologic significance for bron chogenic carcinoma—a corollary which has not been suf ficiently emphasized It is that chronic inflammatory disease *per se* likewise must have little or no etiologic significance for it is difficult to imagine more intense or protracted fibrosing pneumonitis than that which accom panies the more severe forms of silicosis It is becoming increasingly clear that the vague concept of chronic irritation" as a cause of cancer so frequently applied in respect to malignant disease of various organs and regions in past years was greatly overstressed The extrinsic fac

tors are now being sought with increasing success among physical and chemical entities

Cobalt, Nickel, and Bismuth

In the Schneeberg mines, bismuth was not suspected as a cause of miners cancer and there have been no subsequent observations which indicate that it is important in respect to bronchogenic carcinoma

Cobalt was given serious consideration for many years, but during the period when the Schneeberg mines were being worked especially for cobalt, it was found that cancer of the lung did not occur in those employed in the cobalt pigment factory as it did in the miners Surveys in 1925 by a special committee of the Labour Office of the League of Nations covering cobalt miners of many geographic areas failed to show increased pulmonary cancer in this group (Hueper[1])

With nickel developments have been somewhat different Barnett[42] in the *Annual Report of the Chief Inspector of Factories for the Year 1947*, stated that forty seven cases of cancer of the nose and eighty two of cancer of the lung had been reported from a nickel works in Britain Amor[43] had dealt with this group in detail These neoplasms occurred in workers engaged in the refining of nickel by the carbonyl process and the incidental production of copper sulfate Although nickel carbonyl is itself a highly toxic substance there was little evidence that it was the responsible carcinogenic agent The sulfuric acid used in the process contained arsenic In the Canadian refineries where the concentrated ore has the same nickel copper, and sulfur content, sulfuric acid is not used and therefore arsenic is not introduced Amor concluded that the evidence is strongly suggestive that arsenic, in combination with a metal—probably copper—was responsible Morgan, in discussing a paper by William E Smith[44] in

1953 was able to bring this account up to the present The sulfuric acid used in this particular refinery has been free from arsenic since 1923 dust preventive measures were improved in 1924 and the wearing of masks was instituted The incidence of bronchogenic cancer appears to have been greatly reduced in men engaged since 1924 Morgan considered that the results offered support to the view that arsenic and not nickel carbonyl was the causal factor If this is true it strengthens the case for arsenic under other circumstances as in the Schneeberg mines Hueper[1] has considered that the evidence for nickel as provocative of lung cancer is well worth further consideration It cannot be summarily dismissed from the list of possible causative factors

ARSENIC

The high arsenical content of the ore in the Schneeberg mines put arsenic under suspicion as a causal factor as soon as the cancerous nature of the miners disease had been established Harting and Hesse,[28] in 1879 as has been mentioned considered the inhalation of arsenical dust to be the chief cause Others thought that the abundantly growing moulds in the damp portions of the mines formed arsines which were inhaled as well as the dust Currie[45] has stated that a typical analysis of Schneeberg mine dust indicated the presence of cobalt arsenide to the extent of 0 19 per cent and that hyperkeratosis of the palms of the hands occurred in the men washing and selecting the arsenical cobalt ores This latter point has not been emphasized by others in discussing Bergkrankheit

It has long been known that arsenic when ingested over a protracted period leads to a characteristic hyperkeratotic pigmented dermatosis upon which carcinoma may develop Neubauer[46] reviewed the entire field of

arsenical cancer and reached the same conclusion as Currie,[45] namely that there is little evidence to indicate that arsenic has been the cause of cancer of the lung at Schneeberg and Jáchymov These miners did not have an unusual incidence of skin cancers Miners and smelters in other regions where arsenic is abundant are not known to have a high incidence of bronchogenic cancer and bronchogenic carcinoma is a rare complication of typical arsenical cancer However Kennaway and Kennaway[13] have collected several apparently isolated examples of concomitant arsenical dermatosis and bronchogenic carcinoma, and of bronchogenic carcinoma after prolonged use of Fowler s solution without skin lesions due to arsenic While such observations by themselves offer no proof of a causal relationship it is important to have them on record in the hope that similar cases will be noted and reported by others

As to the allegation that the carcinogenic effect of certain tars is actually due to arsenic Hieger[47] has stated that the minute arsenic content of various tars bears no relation to their individual carcinogenic potency

Hill and those associated with him[48] found an apparently significant increase in cancer deaths among the production workers in a factory handling inorganic compounds of arsenic Dust from sheep dip powder was the particular hazard and skin and lungs were the affected organs However, no case of pulmonary cancer was detected in the working personnel during the investigation Even with these comparatively negative observations I am not prepared to drop arsenic entirely from the list of possible environmental factors at Schneeberg Perhaps when inhaled in even small amounts over a long period arsenic may have a conditioning or synergistic effect upon bronchial epithelium Further reference to arsenic must

be made under the topics of general atmospheric contamination and of possible carcinogens in tobacco smoke

IONIZING RADIATIONS

It will be recalled that the pitchblende from which the Curies isolated radium came from Joachimsthal and that Uhlig[29] in 1921 recorded in medical literature a suggestion from a non medical source that Bergkrankheit depended upon the radioactivity of the miners environment After radium became commercially important about 2 gm was produced each year at Joachimsthal Investigation showed that radioactivity in the mines depended upon radium emanation (radon) in the air and water *and upon the radium content of the ore Both of these* varied greatly in different portions of the mines and frequently radon was in excess of that which would have been in equilibrium with the local content of radium indicating the probability that other ore bodies were considerably richer in radium Radon entered the body by the inspired air and by ingested water Radium was taken in as a constituent of rock and ore dust

In environmental radioactivity there seemed to be a highly probable explanation for the prevalence of bronchogenic carcinoma in Schneeberg and Joachimsthal This appeared all the more impressive when physical investigations were published and as was the custom the results were expressed in Mache units * Ludewig and Lorenser[19] found values up to 50 Mache units in the air *in* the Schneeberg mines The average was considerably low

* 1 000 Maché units denotes the amount of emanation in equilibrium with $\frac{1}{2\,000}$ mg of radium 1 microcurie = 2 670 Maché units (Stedman s *Medical Dictionary* 13th edition William Wood & Company)

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er, but a high value was found in the mine known locally as the death mine because of the high mortality of its workers Other biophysical studies followed, and numerous articles appeared in most of which the authors accepted the importance of radium emanation Rajewsky,[50] in 1939, found values in air in the mines up to 22 7 Maché units and in mine water up to 183 units He not only measured environmental radioactivity but also that of the breath, urine and sweat of the miners before during and after working He concluded that it could no longer be denied that injury through breathing the emanation laden air of the mines *was at the very least one of the* causes of Schneeberg cancer

Two years later Behounek and Fořt[51] reported upon similar biophysical investigations of the Joachimsthal area They found that the emanation content of the air in the mines had been improved over previous findings by dilution with outside air through better ventilation High values were found for the water in the mines and for the rock A systematic investigation of the radioactivity of the lungs and vertebrae of necropsied miners was included The time element of exposure appeared to be extremely important and they suggested 10,000 hours of exposure as the critical limit Among their conclusions are found the statements that radiation from inspired emanation was determinative for the origin and development of the disease, and that radiation from the deposit in the body of more permanent sources of radiation was not significant in promoting cancer They believed that the mechanical effect of the dust increased the sensitivity of lung tissue to radiation

In 1944 a somewhat different conclusion was reached by Lorenz[5] after a critical review of all available clinical, biophysical, and experimental data In his opinion, the

claim that radon is the sole cause of lung cancer of the miners of the Erzgebirge cannot be sustained He closed his discussion with a suggestion of hereditary susceptibility as a result of inbreeding but admitted the lack of statistical evidence Obviously hereditary susceptibility likewise could not be the sole factor since the local inhabitants not connected with mining apparently have no more pulmonary cancer than the general population

The significance of irradiation in respect to pulmonary cancer has not been determined by experimental methods, notwithstanding many attempts and it is probable that the answer will not be found by animal experimentation Apparently the "latent period" so significant for man cannot be duplicated in small animals

Ionizing radiation cannot be dismissed lightly Under other circumstances and for other systems and organs its cancer producing effect has been proved and accepted Sarcomas of bone and other supporting tissues carcinomas of skin and mucous membranes and the leukemias are particularly the forms of cancer which can be attributed to radiation That similar endemic carcinoma has not been found in other geographic areas in which radioactive minerals are present may be due at least in respect to recently opened uranium projects to the fact that insufficient time has elapsed Martland's[63] dial painters must have inspired radon as well as ingested radium salts but so far as I know bronchogenic carcinoma has not been observed in that group Hueper[64] has invited attention to the many and varied applications of sources of radiation in modern living Continued vigilance will be needed to detect environmental hazards It is significant that responsible biophysicists have repeatedly lowered the level of permissible total body irradiation per day

As to the miners of Schneeberg and Jáchymov I must

continue to include ionizing radiation whether from radon or radium, among the limited group of factors still under suspicion as inducing bronchogenic carcinoma

SCHNEEBERG AND JÁCHYMOV IN RETROSPECT

The light from the diligent investigation of causal factors in neoplasia which characterizes our era can now

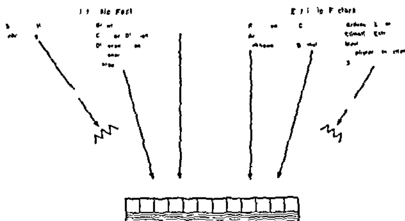


FIGURE 13 Schematic summary of possible causal factors of carcinoma in the Schneeberg miners The device below indicates the bronchial mucosa The interrupted arrows come from factors which have been eliminated as causes The other factors named must remain under consideration

be turned on the Bergkrankheit of Schneeberg and Jáchymov, but neither the experience of 500 years nor the methodology of modern exploration of industrial hazards has provided a fully satisfying answer The evidence may be summarized as follows

Intrinsic Factors The basic intrinsic factors promoting cellular reproduction and growth are ubiquitous A spe-

cific intrinsic factor which has been segregated or emphasized by inbreeding can be excluded The possibility of an unknown intrinsic factor particularly of a sex specific character, must be recognized.

Extrinsic Factors Excluded are the general factors of heavy labor climate infective pneumonitis and pneumoconiosis in the general sense Compounds of cobalt and nickel remain as remote possibilities Radioactivity and arsenic are of primary interest Because no one agent has satisfied critical studies, the way is open for the discovery of causal factors not yet recognized The sequential, additive or synergistic effect of multiple factors is certain to receive increased attention

IV

THE SECOND THEME THE SEARCH FOR THE CAUSES OF INCREASING PULMO NARY CANCER IN THE TWENTIETH CENTURY

MINERS AND PENSIONERS continued to die at Schnee berg and Joachimstal and continued scientific inter est in this unique occupational cancer was evident from the numerous published studies of suspected causal fac tors but in the medical world at large not too much con cern was felt over this apparently local problem However, in the second quarter of the present century it was re luctantly admitted that there was an alarming increase in bronchogenic carcinoma in almost all countries in which vital statistics were collected The local problem had be come universal throughout the industrialized portions of the world

The time at which this change began is somewhat in definite and differed regionally In a general way it can be seen in retrospect that the increase was well under way before 1925 and was beginning by 1910 or even earlier The then current biologic concept was that the proclivity of an organ to develop a neoplasm was a rela tively stable attribute which if changeable at all would change only in the course of biologic time and over sev eral or many generations This was the reason for the reluctance to accept a fact which was becoming increas ingly obvious--that within one lifetime a form of cancer which had been considered very rare was becoming very common When that conclusion could no longer be de

nied the necessity for searching for the cause became all the more urgent That search still continues and certain social occupational and endemiologic factors have been investigated with varying results In the following sections these factors will be presented

INFECTIVE PNEUMONITIS

Because the increased incidence of pulmonary cancer became evident after the great pandemic of influenza and post influenzal pneumonia of 1919 and 1920 the possibility of a causal relationship was a natural assumption Numerous papers discussed this matter and particularly in Europe post influenzal pneumonitis was accepted as the cause of the increase Patients were questioned as insistently in regard to previous pulmonary disease and the elapsed interval since such illness as they are now questioned about their use of tobacco It is unnecessary to review the medical literature on this question for our present purposes Reflection then as now should have served as a reminder that there had been other great pandemics of influenza after which cancer of the lung remained a rare disease that pneumonitis as the sole cause left the riddle of male preponderance unexplained and that the increase in cancer of the lung was becoming evident even before 1919 1920

Although pandemic influenza and pneumonia must be discarded as a cause of the increase in bronchogenic carcinoma there are occasional instances in which chronic pneumonitis seems to be important When a squamous celled carcinoma develops in the wall of a bronchiectatic abscess following metaplasia of the original columnar epithelium to squamous it is reasonable to think of the inflammatory disease as a cause of the cancer Actually it may not have been the ultimate cause but may have

been causal to the extent of inducing the proliferation of cells which were so conditioned as to be vulnerable to the factor which originated irreversible proliferation

Increased Liability to Pulmonary Cancer in Occupational Groups

Investigation of the liability of those engaged in particular occupations should be helpful in indicating presumptive causes of cancer of the lung In view of the high total incidence no one occupation, as such can be of great importance in determining the total picture, but it might be of extreme importance if it furnishes the clue to a significant cause of wider application

Conclusions drawn from apparent occupational concentration of cancer of the lung are subject to many statistical hazards Fundamental is the fact that pulmonary cancer is widespread and the more the population is subdivided the greater becomes the risk of distortion of statistical results by chance distribution Within a particular occupational group there are usually functional subdivisions for which the hazards are entirely different For extrinsic factors which are of accepted importance there is a long latent or lag period between the first exposure and the first signs of cancer Therefore the patient may have changed occupations repeatedly during that time The occupation recorded at the time of diagnosis or of death may not be the one which entailed a special hazard These are some of the reasons why occupational studies of cancer are difficult and why conclusions derived from them must be accepted with caution

There are several occupations in respect to which there is evidence of special liability to pulmonary cancer Those with particularly strong documentation are discussed briefly in the paragraphs which follow

Foundry Workers and Metal Grinders In view of the concentration of the cutlery industry in Sheffield the results of a study by Turner and Grace[55] assume special significance However this dealt with cancer deaths between 1926 and 1935 when the incidence of cancer of the lung was far below its present level During that period there were in the Sheffield area 3 861 deaths from cancer in an average population of 178 559 males over age fourteen Of the cancer deaths 9 6 per cent were from cancer of the lungs and bronchi The working male population and also the deaths from cancer of the lungs were tabulated under thirteen occupational categories The lowest incidence was found in the group of professional commercial financial and clerking males This was considered as the control or base figure and given a value of 100 per cent Warehousemen and packers showed no significant variation (102 per cent) from this base but metal grinders were 133 per cent and foundry workers and smiths 145 per cent above the basal group The authors concluded that in Sheffield a significantly excessive mortality from cancer of the respiratory tract was found in engineers foundry workers and metal grinders and in no other occupational groups

Production and Processing of Chromates That environmental factors in the chromate industry are productive of bronchogenic carcinoma is now well established In 1936 Alwens Bauke and Jonas[56] noted the excessive frequency of this condition in workers in the heavy chemical industry of Ludwigshafen and Griesheim They considered chromate dust to be the chief cause In the occupational group which they studied there appeared to be a latent period of from twenty two to forty years between beginning work with chromates and the development of carcinoma The average period was thirty-one years

Observations similar to those in Germany were subsequently made in the United States Machle and Gregorius[4] in 1948, reviewed the experience of seven plants engaged in the extraction and processing of chromates from ore They found that in this industrial group, lung cancer comprised 60 per cent of all cancers as compared with an expected ratio of 9 per cent The crude death rate for cancer of the lung was twenty five times greater than that which was then considered normal. These authors found some evidence suggesting that monochromates were responsible Imprescia[35] found seven cases of primary lung cancer in a chromate plant with 400 employees This incidence was all the more significant because the annual labor turnover was 40 to 50 per cent in this plant, while the average exposure of those who had carcinoma was sixteen years Mancuso and Hueper,[39] in a thorough appraisal of the health hazard in one chromate plant, showed that the ratio of lung cancer deaths to all deaths of chromate workers was approximately fifteen times greater than that of the general population in the same county The geometric mean latent period for respiratory cancer in these workers was 10 6 years somewhat shorter than had been indicated by earlier surveys These authors considered that insoluble chromium compounds, such as the dust of the chromite ore itself, might be causative

In an industry wide study of chromate workers for an eleven year period based on the morbidity and mortality of those enrolled in sick benefit associations, Brinton Frasier, and Koven[40] found about twenty nine times as many deaths due to respiratory cancer as would have been expected in those of the same age in the general population Another comprehensive study of the abnormally high prevalence of pulmonary cancer in the chromate industry in the United States is included in a monograph by Gafa

fer and associates[61] In this report the suggestion is made that the failure of Bidstrup[6] to find a significant inci dence of bronchogenic carcinoma in 724 workmen in the British chromate industry may have depended upon a specific difference in technical procedures in Britain as compared to Germany and the United States If so this affords an excellent example of the possibility of prevent ing bronchogenic carcinoma by suppressing an environ mental factor

Processing of Asbestos Asbestosis a special form of chalicosis results from the inhalation of finely divided asbestos fibers However asbestos is not a single sub stance[63] The term can be applied to any fibrous silicate of which there are many, and these differ both chemically and physically Since pneumoconiosis due to asbestos can be diagnosed microscopically by the characteristic asbes tos bodies morphologic recognition of the coincidence of asbestosis and pulmonary cancer in necropsy and surgical material is on more secure ground than would be true for most dust diseases

The earlier literature on asbestos as a causative factor for cancer of the lung was reviewed by Hueper[1] in 1942 and again in 1952[64] In the later report he collected about sixty eight examples of the concomitance of these two conditions These were described as single cases or as small groups by many authors However Barnett[4] in an analysis of deaths in England and Wales which were at tributed to industrial hazards found that of 235 in which asbestosis had been established there was concomitant cancer of lungs or pleura in thirty-one (13 2 per cent) This appears to be significant in the over all picture and, from the mortality figures two additional items can be derived which indicate the importance of asbestosis Of 128 male deaths, in twenty two (17.2 per cent) asbestosis

was complicated by carcinoma of the lungs or pleura, and of 107 female deaths nine (8 4 per cent) were similarly affected The ratio of the percentages is almost exactly 2 1, whereas a much greater male preponderance is usually found in necropsy material (See Sex Incidence, p 17) Again, the mean age at death of the males with asbestosis and carcinoma of the lung was 55 2 years and of the females 44 6 years The mean duration of exposure was 20 1 years for males with carcinoma and 7 6 years for females It seems probable that the women had more hazardous assignments Moreover, asbestos, or some factor associated with asbestosis gave an incidence of pulmonary cancer by percentage ten times that found in fatal cases of silicosis (ninety one pulmonary cancers in 6 884 cases, or 1 32 per cent[4]) and in so doing lung cancer was caused to appear more often and earlier in females than is true of bronchogenic carcinoma in general This indicates that *maleness* as a cause of pulmonary cancer may be found to be of little significance intrinsically, but only an attribute associated with particular extrinsic factors

In 1943 Wedler[65] had anticipated the conclusions of Barnett[12] in respect to the proportionately increased incidence of bronchogenic carcinoma in women with asbestosis and also in regard to the earlier average age for the recognition of cancer in that sex He found cancers of squamous celled type most abundant Between beginning work with asbestos and the recognition of carcinoma, intervals of twelve to forty two years were noted He found also that the first clinical evidence of carcinoma might *appear many years after exposure to asbestos dust* had ceased He was convinced that cancer of the lung in an asbestos worker should be considered a compensable occupational disease

There has not been unanimity of opinion in respect to *the causal role of asbestos On both statistical and ex*perimental grounds, Vorwald and Karr[40] concluded that inhaled dusts except those containing recognized carcino genic substances such as radium and tar cannot be considered of significance in the causation of pulmonary cancer Their experimental evidence included 235 guinea pigs which had been made to inhale asbestos dust, and in which no pulmonary tumors were found Such experi ments on laboratory animals necessarily of short duration compared to the working period of man do not create comparable conditions Hueper[54] has recently pointed out that clinical observations made on living asbestos workers in general, have little evidential value and should not be used to discredit other evidence of a causal relationship Such mass statistics do not take into account a probable effective threshold of exposure and are diluted by the inclusion of workers without asbestosis It is also possible that the chemical nature of particular kinds of asbestos *or the prevailing size and length of inhaled fibers* may cause a real difference in the frequency with which car cinoma develops

In connection with a case report and survey of the lit erature Isselbacher Klaus and Hardy[68] prepared Table V They stated somewhat guardedly

> Our conclusion at present is in favor of the concept that the association of bronchogenic carcinoma with asbestosis is more than coincidence

They also referred to the fact that in contrast, bron chogenic carcinoma is associated with silicosis only ap proximately to the degree that it occurs in the general population

The weight of evidence seems heavily in favor of

assigning etiologic significance to asbestosis when it is found in association with pulmonary cancer

TABLE V
INCIDENCE OF ASBESTOSIS AND CARCINOMA OF LUNG

Author	*Number of Deaths With Asbestosis*	*Number of Deaths Due to Cancer of Lung*	*Incidence*
			%
Merewether	235	31	13 2
Wedler	92	15	16 3
Wyers	115	17	14 8
Lynch Cannon	40	3	7.5
Gloyne	121	17	14 1
Total	603	83	13 8

Reproduced by permission from Isselbacher Klaus and Hardy *Am J Med* *15* 721 732 1953

Compounds of Nickel, Arsenic, Ionizing Radiation Since salts of nickel arsenic containing ores and ionizing radiation were all in the physical chemical environment of Schneeberg and Jáchymov, these factors have been discussed in an earlier section (pp 40-46) All continue to play an important part in modern life—radioactivity to a rapidly increasing extent The latter two, particularly, remain under suspicion as possibly having a share in creating the current problem of bronchogenic carcinoma

A HISTORICAL INTERLUDE

Again we turn to medical history to seek the origins of what is now a vast store of knowledge about more than 700 condensed ring hydrocarbons as proved or suspected causal factors in cancer The hazards therefrom have been found in the domestic and social habits of man, in occupations in accidental exposures, and in the inevitable atmospheric pollution which comes with the concentration of human beings in a highly industrialized and highly motorized manner of living

Ideally the combustion of organic matter results in complete oxidation with water (hydrogen oxide) carbon dioxide mineral ash (chiefly oxides) and a small amount of other oxides as the products of its carbohydrate and hydrocarbon complexes It has been the good fortune of man that such complete oxidation is rarely achieved under natural conditions and he has had as his servants a series of resources ranging from natural gas through intermediate petroleum products paraffin tars and pitches to coal and the diamond These servants and their allies are also sources of danger Because complete combustion is uneconomical or impossible in releasing energy as heat or power man adds smoke smog soot volatile products and carbonaceous dusts to his environment Among these substances or incorporated in them or adsorbed on their surfaces or arising as secondary products of their further oxidation are proved chemical carcinogens Much of the proof has been secured by cutaneous application or subcutaneous injection with mice as the subjects

It should be clearly understood that as of the present no chemical carcinogen has been proved to be the cause of pulmonary cancer in man It is difficult to conceive how such proof could be adduced Perhaps it can be approximated by statistical analysis of association with elimination of other suspected causes

Since bronchial epithelium can undergo metaplasia to a squamous type and squamous celled carcinoma can arise from bronchial mucosa the clinical and experimental observations of squamous celled carcinoma of the skin induced by environmental factors are not too far removed from our field of interest

Percivall Pott and Chimney-Sweeps Cancer Percivall Pott[70] wrote in 1775 after referring to occupations precipitating lead colic

THE

CHIRURGICAL WORKS

OF

PERCIVALL POTT, F R S

AND

SURGEON TO ST BARTHOLOMEW'S

HOSPITAL

A NEW EDITION WITH ADDITIONS

IN THREE VOLUMES

VOL. III

A certis [illegible] explorat[illegible] [illegible]
Experientia in ipsis [illegible]
[illegible] Agricolam [illegible] Gubernatorem [illegible]

A Corn Cels[illegible]

LONDON

Printed for T Lowndes J Johnson G Robinson T Cadell
T Evans, W Fox J Bew, and S Hayes

MDCCLXXXIII

FIGURE 14 Title page of the third volume of *The Chirurgical Works of Percivall Pott* in which reference to chimney sweeps cancer appears

C A N C E R

S C R O T I.

RAMAZINI has written a book de morbis artificum, the Colic of Poictou is a well-known diſtemper, and every body is acquainted with the diſorders to which painters, plummers, glaziers, and the workers in white lead, are liable: but there is a diſeaſe as peculiar to a certain ſet of people, which has not, at leaſt to my knowledge, been publicly noticed, I mean the chimney-ſweeper's cancer

It is a diſeaſe which always makes its firſt attack on, and its firſt appearance in the inferior part of the ſcrotum, where it produces

FIGURE 15 The page from *The Chirurgical Works* on which Percivall Pott introduced the topic of chimney sweep's cancer of the scrotum

> but there is a disease as peculiar to a certain set of people which has not, at least to my knowledge been publicly noticed I mean the chimney sweepers cancer

After describing the appearance, course, and surgical treatment of cancer scroti, he continued

> The disease, in these people seems to derive its origin from a lodgment of soot in the rugae of the scrotum

This observation of an occupational environmental cancer was basic for present day knowledge of chemical carcinogens Soot is not finely divided carbon alone, but combines other products of incomplete combustion of organic matter The broadening line of descent of knowledge of extrinsic factors causative for cancer can be traced from Percivall Pott and his chimney sweeps cancer, through the occupational tar cancers to dibenzanthracene methylcholanthrene and other chemical agents so potent for the production of cancer that the experimentalist now can produce a cancer to order in a suitable laboratory animal

Neither knowledge that many scrotal cancers were occupational nor regulatory legislation based thereon brought about a dramatic relief from chimney sweeps cancer Regulations were poorly enforced and the long latent period before the appearance of cancer gave a false sense of security In an analysis of deaths attributed to scrotal cancer Henry and Irvine[71] reported, 160 years after Percivall Pott that in England and Wales between 1911 and 1930, there were eighty two deaths from this disease in chimney sweeps ranging in age from thirty five to eighty four years (average 61 6 years)

Kangri Carcinoma By 1910 Dr Ernest F Neve,[72] then surgeon to the Kashmir Mission Hospital, had recognized and interpreted correctly as due to an environmental fac-

tor a squamous celled carcinoma which came under his observation During twenty five years 1 720 malignant neoplasms were removed in that hospital of which no less than 848 were epitheliomas" of the thighs or abdomen Those who developed the lesion were all users of the kangri a portable fire basket carried under the clothing In a squatting position it might rest against the inner surface of the thighs as well as the abdomen Epithelial proliferation hyperkeratotic areas mottled pigmentation and finally, carcinoma developed This malignant lesion was twice as common in males as in females and the average age at which it was manifest was fifty five Metastases to regional lymph nodes were common Neve thought that heat must be the provocative agent but in a later report[13] he wrote "Volatile substances products of combustion auxetics may possibly play a secondary part

In the light of present knowledge heat as such would be relegated to a minor rôle In the use of the kangri conditions were ideal for incomplete combustion a confined space beneath heavy clothing with restriction of oxygen and retention of soot and tarry products a fire which of necessity must smoulder or glow and never burst into flame Thus it has been recognized (Hueper[1]) that the resulting cancers are grouped more appropriately with the soot or tar cancers The kangri carcinoma of Kashmir provides a remarkable and instructive example of the production of squamous celled carcinoma of the skin by an extrinsic agent This example is all the more impressive because of its high incidence in the group exposed and because it involved an anatomical site in which such cancer is otherwise of rare occurrence

Tar Cancers and Identification of Cancerogenic Hydrocarbons Even a cursory survey of the historical pathway from Percivall Pott to the current investigation of carcino-

genic agents produced by incomplete combustion must include reference to the clinical recognition of tar and pitch cancers and of the successful identification of some of the causative agents Brilliant achievements have made possible the synthesis of hundreds of organic compounds of proved cancerogenic action in laboratory animals As a result the investigator of today can, practically speaking, create and propagate a malignant neoplasm to order This availability of biologic tools for investigation goes far to refute the careless phrase, "the cause of cancer is not known"

The first description of occupational cancer of the skin from tar or pitch is attributed to Volkmann[74] (1875) but it was not until the early years of the present century that case reports became frequent (Literature by Hueper[1]) Yamagiwa and Itchikawa[75] had succeeded in producing cancer of rabbits ears by inunction with tar in 1914 and 1915 but this information was not generally available until several years later[76] By fractionation of carcinogenic tar by systematic investigation of pure substances known to be present in tar or capable of derivation therefrom, and by application of fluorescent spectroscopy because the carcinogenic fraction of tar was fluorescent, Kennaway,[77] Mayneord[78] and Cook, Hewett, and Hieger[79] with others established the importance of 1 2 benzanthracene and of 3 4 benzpyrene among the cancerogenic components of particular English coal tars and pitches

These brief references to the historical background of the clinical recognition and physicochemical identification of the cancerogenic products of incomplete combustion make possible the discussion of another occupational hazard in respect to cancer of the lung

Cancer of the Lung in Gas Workers in England and Wales From an analysis of death certificates in England

and Wales upon which the cause of death had been certified as cancer of the lung Kennaway and Kennaway[13] found that the number of deaths attributed to gas workers appeared to be well in excess of the general incidence for employed males Since the actual number employed or pensioned had to be determined by deduction further investigation was indicated This is a difficult field because of the varied activities in the artificial gas industry some of which require no special contact with carcinogenic components of tar and other wastes Such a study has been completed by Doll[80] (1952) who found that mortality from all causes among the pensioners of a large London gas company was approximately that which would have been expected in a comparable fraction of the general population However the mortality from all cancer was 181 per cent of that expected and the excess was due to increased deaths from cancer of the lung Of these there were 25 whereas the computed expectation was 13 8 The excess mortality occurred principally among employees engaged in the production of illuminating gas and in the treatment of waste products of gas plants While no large body of evidence has been accumulated such figures suggest that products of incomplete combustion as found in some gas and tar operations may be causal for bronchogenic carcinoma just as such products were shown to produce cancer of the skin If fully confirmed such information will be of even greater value in its broad implications as to the etiology of cancer of the lung than in indicating the means by which the incidence of that condition can be reduced in the limited group of gas workers

Atmospheric Pollution

Important as the knowledge may be for the particular groups concerned it is evident that the special liability to cancer of the lung on the part of asbestos and chromate

workers, some gas plant employees, metal processors, and other relatively small occupational groups is an inadequate explanation for the increase in this disease in the

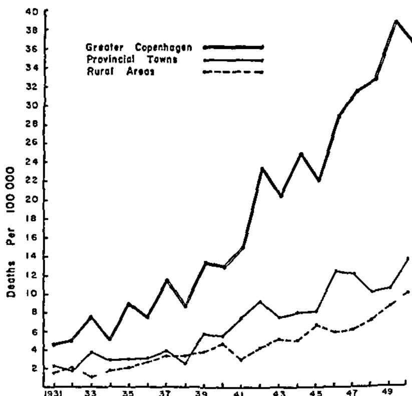


FIGURE 16 Comparative mortality from cancer of the lung in greater Copenhagen provincial towns and rural areas of Denmark [83] (Redrawn by permission from Clemmesen Nielsen and Jensen *Acta Unio Internationalis Contra Cancrum* 9 603 636 1953)

last forty years The magnitude of the increase suggests that one or more cancerogenic substances may have entered the human environment as atmospheric contaminants within the last half century There are numerous avenues by which exploration of such a hazard has been at

tempted and comprehensive surveys of current opinion can be found in the reviews of Hueper[81] and of Hammond[8]

Effect of Density of Population and Industrialization There is statistical evidence of a significant positive correlation between density of population or, particularly, density of occupied dwellings and of industrialization and the incidence of cancer of the lungs Mortality rates from this cause are invariably higher in urban than in rural communities It is recognized that there may be

TABLE VI
RELATIVE MORTALITY FROM CANCER OF THE LUNG AND LARYNX IN ENGLAND AND WALES FOR 1946 1949 BY CLASSIFIED AREAS (LONDON = 100)

	Cancer of Lung		Cancer of Larynx	
	Male	Female	Male	Female
London	100	100	100	100
Other large towns	78	73	60	182
Other urban districts	63	61	68	170
Rural districts	43	54	59	239

Reproduced by permission from Kennaway and Waller[11] *Acta Unio Internationalis Contra Cancrum* 9 485-494 1953

other variables influencing accuracy or completeness of reporting but the differences are too great to be explained entirely on that basis From various available reports I select first that of Clemmesen Nielsen and Jensen[83] from which Figure 16 is redrawn This graphic presentation of the marked difference in mortality from cancer of the lung in Greater Copenhagen as compared to the provincial towns and rural areas of Denmark is self-explanatory In all fairness the authors state that conditions in Denmark are such that it seems impossible to explain how atmospheric pollution could cause the differences"

Similar results were obtained by Kennaway and Wal

ler[11] for England and Wales As is shown in Table VI, the relative mortality from cancer of the lung in rural districts was less than one half for males and only slightly over one half for females of that for each sex in London Other

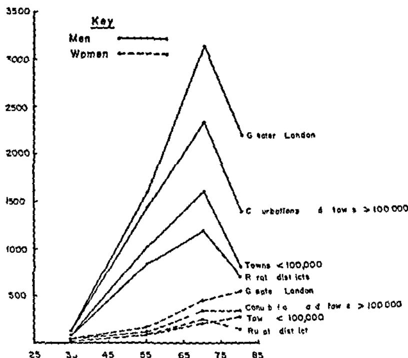


FIGURE 17 Death rate from cancer of the lung by ages and by sex in different areas of England and Wales 1950 This illustrates the higher incidence associated with increased density of population[16] (Redrawn by permission from Doll *Brit M J* 2 521 527 585 590 1953)

large towns as a group and other urban districts yielded intermediate figures For as yet unexplained reasons, a reverse relationship was found for cancer of the larynx in women This apparently discordant note may prove significant as extrinsic factors are determined more precisely It at once points up the fallacy of grouping diseases of the respiratory tract in one category

Doll[16] apportioned the death rates from cancer of the lung according to four areas as to density of population rural districts towns of less than 100 000 conurbations and towns of more than 100 000 and greater London With further division according to age and sex, the resulting curves are presented in Figure 17

For the United States Hammond[8] has reported that death rates for males from cancer of the respiratory system were in the ratio of 9 4 for urban and rural districts and for females in the ratio of 5 4 These ratios were based on 1944 data supplied by the Bureau of the Census and do not necessarily reflect the ratios which exist today The following quotation from Hammond indicates his cautious evaluation

> There is still considerable doubt whether the urban rural difference is real or whether it is due to errors in diagnosis and artifacts resulting from the methods used in reporting place of residence at time of death Until this matter is cleared up as it should be within a year or two one should be cautious in drawing conclusions based upon this evidence

Reasons which have been adduced for the higher death rate in urban districts include (1) Better diagnostic facilities *in more populous districts (2) tabulation by place* of death rather than by actual residence (3) differences in smoking habits and (4) atmospheric differences The qualitative and quantitative differences in respect to medical care between urban and rural areas are rapidly disappearing in those regions to which reference has been made The error introduced by death certificates giving place of death can be corrected by adequate investigation Differences in smoking habits as of today do not seem very important but as will be brought out it may be necessary to consider what differences may have exist

ed twenty or more years ago Our present concern is with atmospheric pollution

Domestic and Industrial Smoke Soot is the chief component of smoke and clinical observations since Percivall Pott have confirmed the cutaneous carcinogenic nature of soot By the use of the fluorescence spectrum, Goulden and Tipler[84] determined the presence of 3 4 benzpyrene in mixed domestic soot from a chimney sweeps stock, with an indicated content of about 300 mg of benzpyrene per kg of soot

There is less visible smoke and soot in the United States and Britain than there was thirty or forty years ago There have been marked changes in the pattern of fuel consumption Coal and wood are being replaced in urban districts by oil and gas for domestic heating and also to a considerable degree in the production of power Electricity supplies light and power When electrical energy is produced in steam plants from coal the fuel is now burned more efficiently and new plants are located in relation to economical transportation of coal rather than to central distribution of electricity In this country the railroads are rapidly shifting from soft coal burning engines to oil burners or to electricity Most of these changes, it would appear are in the direction of reducing atmospheric pollution by smoke However that may not mean an equal reduction in carcinogenic components, and changes for the better if such there are cannot affect the incidence of cancer of the lung for years to come The incomplete combustion in public and private incinerators is a newer factor in augmenting atmospheric pollution Stocks[85] was impressed by the smoke hazard and stated that there appeared to be a general tendency for mortality from cancer of the lung to increase with the total number of chimneys in a community until the dwellings exceeded 100 000, after which other factors appeared to be additive

Soot and other products of incomplete combustion have not been proved to be causes of pulmonary cancer This possibility is still in the stage of hypothetic exploration, as is true of others which must be mentioned

Dust and Fumes from Bituminous Surfaced Roads It can be shown that the rise in pulmonary cancer has been contemporaneous with the growth of highway systems with oiled, tarred or asphalted surfaces Bituminous products used for this purpose are known to contain carcinogenic agents and particulate matter is abraded from the road surface to be disseminated as dust To this dust is added carbon black from automobile tires In spite of continued interest in this matter for many years no important evidence has been advanced that bituminous roads have contributed specifically to the incidence of bronchogenic cancer This also is a field for exploration of hypotheses

Exhaust Products from Internal Combustion Engines There is no more conspicuous change in the pattern of human living during the period of the rise of bronchogenic carcinoma than that afforded by the ubiquity of self propelled vehicles Circumstantial evidence of the same character as that advanced in respect to cigarette smoking can be used to cast suspicion on the automobile (1) There is remarkable chronologic parallelism between the production and use of automobiles and the increase in cancer of the lung (2) The concentration of automobiles in urban and industrialized areas is in accord with the higher incidence of bronchogenic cancer in such communities (3) Sufficient time has elapsed as of today, since the automobile became of common use to satisfy the requirement of a latent period

Kotin[86, 87] and his associates have included vehicular exhausts from both gasoline and diesel engines in a systematic search for the sources of carcinogenic air pollut

ants in the Los Angeles area Their interest was particularly in the aromatic polycyclic hydrocarbons and from the exhaust of a gasoline engine they obtained pyrene 3 4 benzpyrene, 1 2 benzpyrene, 1 12 benzperylene capo nene, anthranthrene and an unidentified yellow crystalline compound While the output of individual hydrocarbons varied somewhat with load and speed, it was found that the worst conditions for a gasoline-propelled vehicle from the standpoint of emission of hydrocarbons occurred during acceleration from low speed In descending order of emission this was followed by idling at a low engine rate, and then by deceleration It will be noted that these determinations have an important bearing on urban driving Under conditions of maximum hydrocarbon production 7 5 mg of pyrene was formed per minute by the engine under test Benzpyrene was found in 10 per cent of this amount Benzene extracts of the particulate phase of the exhaust products produced cutaneous papillomas and squamous celled carcinomas of the skin in C57 black mice in long term painting experiments

Three agents known to be cancerogenic are present in the atmosphere of densely inhabited areas Reference to each of these has run like a thread through the preceding discussion They are arsenic, ionizing radiation, and benz pyrene

Arsenic Presumably atmospheric arsenic comes chiefly from the burning of fuel the smelting of ores and the use of insecticides Goulden, Kennaway and Urquhart[88] determined the arsenic in suspended matter in the air at eight localities in England and in the winter and summer Their results are presented in Figure 18 redrawn from their report The amount found averaging about 0 07 μg per cu m computed as As_2O_3 was often only twice that found in the blank control so no high degree of accuracy

was claimed It will be seen that the values presented are highest for London and uniformly higher in winter than in summer reflecting fuel consumption The authors computed that a man breathing 20 cu m of air a day would

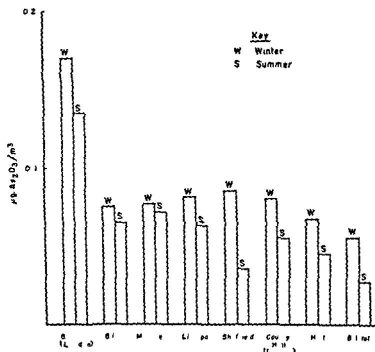


FIGURE 18 Mean seasonal variations in arsenic content of air at eight stations in England While the content of arsenic is very small, it is invariably higher in winter than in summer [88] (Redrawn by permission from Goulden Kennaway and Urquhart *Brit J Cancer* 6 1 7 1952)

inhale but 0 5 mg of As_2O_3 per year Considering known industrial hazards this amount would seem insignificant unless it plays an additive or synergistic role in association with other carcinogens

Ionizing Radiation Apart from special local environ

mental conditions which might lead to unusual exposure to radioactivity, there is measurable atmospheric radio activity Presumably this is derived from the decay of radioactive materials in the earth s crust If so, it can be assumed to have been fairly constant in kind and quantity over long periods and this would seem to exclude it from participation as a cause of the current increase in lung cancer Dawson[89] found no great difference in the open air in cities and in the country, but there was marked day to day variation out of doors which depended upon wind The more stationary the air, the greater was the radioac tivity In closed spaces such as an underground air raid shelter the amount might be several hundred times that found in the open street For instance, the average value found in an air raid shelter in central London was 11 796 10^{12} curies/cu m and at a nearby control point in the open, 96 5 10^{12} curies/cu m Even the higher of these values is well below the limit of tolerance for man

Dawson[89] has brought together the determinations of other observers and discussed the dosages deduced there from He very properly called attention to special risks in hospitals laboratories and isotope installations of all types but so far as general atmospheric radioactivity is concerned there is no basis for considering it of signifi cance in causing pulmonary cancer

Benzpyrene in the Atmosphere Since benzpyrene was found in soot (Goulden and Tipler[84]), its presence in air without visible smoke was to be expected Waller[90] esti mated the benzpyrene content of filters through which air had been drawn at ten stations in Great Britain The mean annual concentration was of the general order of 2 7 µg per 100 cu m of air The seasonal variation was greater than the difference between stations The concen tration rose sharply during the winter indicating the con

tribution from space heating sources and there was also a tendency for the mean annual values to increase with the size of the community

Kotin Falk Mader and Thomas[86] found 3 4 benzpyrene present in the air of Los Angeles in an amount of only 900 µg per 1 000 000 cu ft (28 300 cu m) The high tumor yield from the painting of extracts of atmospheric residue on C57 black mice in spite of the low benzpyrene content was thought to indicate either the presence of unknown substances of high carcinogenic potency or the production of other carcinogens during the oxidation of known atmospheric hydrocarbons

The emphasis which has been put upon the benzpyrene content of smoke soot road dust and air depends in part upon the extensive knowledge of its fluorescence spectrum which has made estimation of very minute amounts possible As a possible cause of cancer of man benzpyrene thus far suffers only from guilt by association and by inference from results of animal experiments I know of no proof that any of the benzpyrenes has caused cancer in man It must be remembered that other carcinogens have been proved to be present in some tars (Berenblum and Schoental[91]) Still more potent carcinogens possibly water soluble may await discovery

Retrospect

In retrospect it has been shown in the search for the causes of the increasing incidence of pulmonary cancer in the twentieth century that certain occupations are or were particularly hazardous This was true of some foundry workers and metal processors of those producing and packaging chromates processing asbestos refining nickel and working with arsenical dust Most of these hazards were preventable with improved industrial practices In

another industrial group, namely, workers with certain tars in gas production and distribution, the greater liability to bronchogenic carcinoma was assumed to be due to exposure to cancerogenic hydrocarbons known to be products of incomplete combustion

The forty years more or less, in which the incidence

Bronchogenic Carcinoma
in the
Twentieth Century

FIGURE 19 Schematic summary of possible causal factors for bronchogenic carcinoma in respect to the increase in the first half of the twentieth century The broken arrows at right and left lead from factors which are believed to have been eliminated from further consideration To be compared with Figure 13

of bronchogenic carcinoma has been rising to an alarming degree has been a period of increased industrialization of changes in commonly used fuels, and of the ascendancy not to say dominance, of the automobile It has been the era of the internal combustion engine These violent changes in the pattern of life (all of which are incorporated in our 'higher scale of living') have accentuated some long suspected environmental hazards and have in

troduced new ones But the cause so far as the general population is concerned has not been clearly established

Another widespread change during the last forty or fifty years has been in the use of tobacco Not only has the consumption of tobacco increased in those regions in which pulmonary cancer has increased but a proportionately greater amount of tobacco is now being smoked and this in turn with a shift from cigars and the pipe to cigarettes During this period also the women of Europe and the Americas have become cigarette smokers An association between heavy cigarette smoking and pulmonary cancer is now being claimed The evidence upon which this is based and possible causal factors provided the relationship should be more than association form the subject matter of the Third Theme

V

THE THIRD THEME TOBACCO SMOKING AND BRONCHOGENIC CARCINOMA

THERE HAS BEEN INTEREST in the possible relationship between smoking and cancer of the lung almost from the time that this neoplasm was recognized Even at Schneeberg we found Harting[28] making inquiry in 1878 as to the smoking habits of an afflicted miner It is easily appreciated that the presence in the airway of the products of slowly burning tobacco should arouse suspicion when cancer develops in that tract It was not long before the possibility of association of the two was under statistical investigation and there have been three methods applied in succession, by which this association has been studied These can be designated, respectively, as the Casuistic, Comparative and Prospective Methods

THE CASUISTIC METHOD

The casuistic method, which depends entirely upon the history of the afflicted patient, is the original approach when a causal factor is suspected but the earlier reporters of collected cases of cancer of the lung were more interested in industrial hazards than in personal habits Some like Perret[60] commented on the excessive use of tobacco in their patients Such observations proved nothing because there was no basis for comparison with the smoking habits of a comparable group from the general population, but they did indicate the need for more critical investigation They seemed to be in accord with earlier observations of the frequency of cancer of the lung in cigar makers and tobacconists generally

The Comparative Method

The comparative method like the casuistic method requires the collection of personal histories as to smoking from those with pulmonary cancer, but it then takes the next step and compares the smoking habits of the cancerous group with those of a non pulmonary-cancerous population as a control Statistical value depends on the size of the respective samples and on the precision with which the control group is selected It must be made truly similar in age sex, and color The value will be further enhanced if the groups to be compared are of similar geographic extraction equally urban and/or rural of similar social status and similarly distributed in diverse occupations In short they should differ so far as can be achieved only in that one group has cancer of the lung and the other does not By personal interrogation the smoking habits of each member of each group are learned as to amount manner and duration of smoking.

There are two general methods by which the control group can be established One is a case by case matching plan utilizing for the control group patients with non cancerous disease, or those with cancer of other areas than the respiratory tract or selected persons from the apparently healthy population This has the advantage of giving opportunity for detailed appraisal of the controls as individuals The second method is to compare the smoking habits of those with pulmonary cancer with the smoking habits of an assumed standard population which in turn has been established by a large scale census The second plan offers the advantage of deriving the control data from a large group who might thereby be more representative of the population at risk Severe critics will insist that one group of human beings can never be truly representative of another group

The first use of the comparative method in connection with smoking appears to have been by Muller[93] who, in 1937, studied the histories of eighty six male patients of the University Hospital of Cologne who had, or had died of, cancer of the lung He divided them into five categories as extreme smokers, very heavy smokers heavy smokers, moderate smokers and non smokers (In the last group

TABLE VII
COMPARISON OF THE USE OF TOBACCO PER DAY BY 86 MALES WITH PULMONARY CANCER AND OF 86 HEALTHY MALES

Smoking Habits	Actual Numbers		Percentage	
	With Cancer	Healthy Controls	Of 86 With Cancer	Of 86 Healthy Men
Extreme smokers*	25	4	29 07	4 65
Very heavy smokers	18	5	20 93	5 81
Heavy smokers	13	22	15 12	25 58
Moderate smokers†	27	41	31 39	47 68
Non smokers	3	14	3 49	16 28
Totals	86	86	100 00	100 00

* Extreme smoker = 10 to 15 cigars or more than 35 cigarettes or more than 60 gm pipe tobacco daily
† Moderate smoker = 1 to 3 cigars or 1 to 15 cigarettes or 1 to 20 gm pipe tobacco daily
(*From Muller*[93])

there were but three) When compared with eighty six healthy men of similar ages there was a marked difference in the trend toward heavy smoking in those with cancer of the lung Muller s summary appears as Table VII It falls far short of proof because it would be extremely difficult to pick a control group of only eighty six without some bias in the manner of selection In the same report Muller stated that the use of cigarettes in Germany had increased more than five fold between 1907 and 1937

Studies employing similar comparative methods have appeared with increasing frequency until there are now about fifteen available with each author striving to make

his control group more truly representative than those of his predecessors With but a few minor exceptions these studies are in agreement that there is an association be tween heavy smoking and pulmonary cancer The actual proportions of those in the various categories has varied considerably in these reports This is to be expected be cause of geographic locations differences in definition of smoking categories and differences in expressing the cigarette equivalent of cigars and pipe tobacco Especial ly important is it to secure the smoking history of each person over a period of many years The non smoker of today may consider his heavy smoking of ten or twenty years ago of no importance and insistent questioning may be needed to bring out the truth

Because of the many minor differences in method and definition it is impossible to bring together in one table the results of all the important comparative studies Par tial compilations can be found in articles by Levin[13] and by Hammond and Horn[94]

As a more modern example of the use of the compara tive method the work of Wynder and Graham[95] (1950) can be cited The smoking habits of 605 patients with cancer of the lungs were compared with those of 780 male patients with other diseases Whereas there were 14 6 per cent non smokers among the general male group there were 1 3 per cent non smokers among male patients with pulmonary cancer There were 54 7 per cent heavy to chain smokers and 19 1 per cent excessive and chain smokers in the non pulmonary-cancer group Correspond ing figures for the pulmonary cancerous group were 86 4 and 51 2 per cent

Doll and Hill[96] (1952) have utilized comparison with both non pulmonary cancerous hospital patients and a sample of the general public in a study of the smoking habits of the respective groups Their comprehensive in

vestigation included inquiry into many aspects of the use of tobacco and extended also into environmental factors other than smoking For our present purposes, their Table V has been rearranged and appears as Table VIII An important feature of the report by Doll and Hill is the segregation and also inclusion of 202 patients incorrectly

TABLE VIII
AVERAGE AMOUNT OF TOBACCO SMOKED DAILY OVER THE 10 YEARS PRECEDING THE PRESENT ILLNESS

*Smoking Habits**	*Men*				*Women*			
	1357 With Lung Carcinoma		*1357 With Other Diseases*		*108 With Lung Carcinoma*		*108 With Other Diseases*	
	No	%	No	%	No	%	No	%
Non smokers	7	0 5	61	4 5	40	37 0	59	54 6
< 5 cigarettes daily	55	4 0	129	9 5	16	14 8	25	23 1
5 15 cigarettes	489	36 0	570	42 0	24	22 2	18	16 7
15 25 cigarettes	475	35 0	431	31 8	14	13 0	6	5 6
25 50 cigarettes	293	21 6	154	11 3	14	13 0	0	0 0
> 50 cigarettes	38	2 8	12	0 9	0	0 0	0	0 0

* 1 oz of pipe tobacco a week = 4 cigarettes a day
Rearranged from Table V of Doll and Hill [96] *Brit M J* 2 1271 1286 1952. Reproduced by permission.

thought to have carcinoma of the lung This group gave histories of smoking habits proportioned as were those of patients with other respiratory diseases with cancer in other sites, and with other diseases in general, but unlike those of patients proved to have pulmonary cancer This shows that the results from the major group were not fallacious because of special selective factors associated with hospitalization for bronchogenic carcinoma or of bias on the part of those interviewing the group having bronchogenic carcinoma

In view of the decisive results quoted from Wynder and Graham [95] and from Doll and Hill[96] and the general agree

ment of their findings with those of Levin[19] and many others it must be concluded that, by the comparative method of statistical study, an association has been dem onstrated between tobacco smoking and carcinoma of the lung The assertion of a relation of association does not necessarily imply a causal relation

In addition to proof of an association between smoking and pulmonary cancer certain miscellaneous data have been established with varying degrees of certainty It is evident that intensity and duration of smoking are very important In the series of Wynder and Graham [93] of 605 patients with cancer of the lung 96 1 per cent had smoked for twenty years or more For an equal weight of tobacco consumed cigarette smoking appeared more significant than pipe smoking A far larger percentage of cigarette smokers than of cigar or pipe smokers admitted that they consciously inhaled smoke Proportionately more non smokers were found among males with bronchial adeno carcinoma than among those having squamous celled and undifferentiated neoplasms Adenocarcinoma of the lung is proportionately more common in women and surveys show that there are far fewer women than men who have been heavy smokers for twenty years or more The infer ence is that extrinsic factors play a much smaller part in the causation of adenocarcinoma than of other forms There is insufficient evidence as yet in respect to a possi ble lessened effect in those who use cigarette holders or filters There is no evidence that lighter fluid in mechani cal lighters is of any importance

THE PROSPECTIVE METHOD

The comparative method is largely historical It is also retrospective and is sometimes referred to by that term The *prospective* method of recent introduction is histori

cal so far as smoking habits are concerned, but looks only to the future for the advent of disease and death

Under the auspices of the American Cancer Society and with the aid of 22 000 volunteer workers, usable questionnaires were secured which gave in adequate detail the smoking characteristics of 187,766 white males between the ages of fifty and sixty-nine The death of any man in her group was to be reported by the responsible worker, after which the cause of death would be learned through official channels The questionnaires were largely completed in the first five months of 1952 An apparent objection to the prospective method was the period of delay before significant results could be known but with such a large initial group the delay was surprisingly short, as will appear

After about twenty months, 4 854 deaths had occurred These form the subject of a preliminary report by Hammond and Horn [67] Of these deaths, 167 were attributed to primary pulmonary cancer The distribution in respect to smoking habits at the time of questioning is shown in Table IX It will be noted that even in this early report the difference in lung cancer deaths between non smokers and regular smokers proved to be statistically significant (P = 0 002 or less) I quote from Hammond and Horn

> The best estimate that can be made at the present time (at the 5% level of confidence) is that lung cancer deaths are from 3 to 9 times as common among men with a history of cigarette smoking as among men who have never smoked regularly and that lung cancer deaths are from 5 to 16 times as common among men who smoke one pack or more per day [as among non smokers]

The prospective method permits the simultaneous investigation of any cause or of all causes of death in relation to the historical attribute (in this instance, *smoking*)

The preliminary report of Hammond and Horn[37] includes "by products" which may be of even greater importance than demonstration of the association of smoking and cancer of the lung Smoking was found to be associated with a considerably higher total death rate, due largely

TABLE IX
LUNG CANCER DEATH RATES BY TYPE OF SMOKING

Type of Smoking at Time of Questioning	*Population at Risk*	*Deaths Attributed to Pulmonary Cancer*	*Death Rate Per 100,000*
Never smoked or occasionally only	44 091	12	27 2
Cigar and/or pipe cigarettes never smoked regularly	35 853	12	33.5
Regular cigarette smoking	107 822	143	132 6
Totals	187 766	167	88 9
Regular cigarette smoking < one pack a day	54 799	62	113 1
Regular cigarette smoking one + packs a day	25 497	61	239.2

Abridged from Hammond and Horn[37] *J.A.M.A* *155* 1316-1328 1954
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to a higher death rate from coronary occlusive disease and from cancer in general as well as cancer of the lung More complete reports will follow

Doll and Hill[38] were already applying the prospective method to British physicians Usable questionnaires were obtained in 1951 from 24 389 male doctors over thirty five years old During the next twenty nine months, the deaths of 789 doctors were reported and of these thirty six were attributed to pulmonary cancer The distribution of these deaths in respect to smoking habits is shown in

Table X The number is small and does not reflect the true death rate for doctors, because it was evident that those who were seriously ill in 1951 did not return questionnaires Nevertheless, the progressive trend toward higher death rates from pulmonary cancer with increased smoking is clearly evident Much more information will be available in the next few years

TABLE X
MORTALITY OF BRITISH PHYSICIANS AS RELATED TO SMOKING HABITS
A PRELIMINARY REPORT

Smoking Habits	Number at Risk Over Age 35	Deaths From Cancer of Lung (29 Months)	Standardized Death Rate From Cancer of Lung Per 1000 Per Annum
Non smokers	3 093	0	0 00
1 14 gm per day	8 431	12	0 48
15 24 gm per day	7 662	11	0 67
25+ gm per day	5 203	13	1 14
Total	24 389	36	0 66 (all groups)

* 1 cigarette = 1 gm 1 oz pipe tobacco a week = 4 gm a day
Rearranged from Doll and Hill " Brit M J 1 1451 1455 1954 Reproduced by permission

If there were hidden fallacies in the comparative or historical method it might be expected that they would be revealed by the entirely different approach of the prospective method However all methods agree in indicating a statistically significant association between protracted cigarette smoking and pulmonary cancer, with the degree of association increasing with the amount of tobacco used While proving association does not prove causal relationship, no one has succeeded in explaining how or why such an association exists if causal factors are not implicated Possible causal factors in tobacco and tobacco smoke are considered in the following sections

Radioactivity of Tobacco Smoke and Tobacco Ash A recent report from the University of Leeds[99] indicates that the average radioactivity of one cigarette approximates that of 25 mg of potassium and that the radioactivity of the ash is of the same order The radioactivity of the smoke from one cigarette is about that of 6 µg of potassium These values indicate that such radioactivity as is present in tobacco remains in the ash Little if any is transferred to the smoke If these determinations are sustained little importance can be attached to the radioactivity of tobacco Of course the possibility of an additive effect is always open no matter how small the increment may be

Arsenic in Tobacco and Tobacco Smoke There has been interest in the arsenical content of tobacco for reasons other than a possible causal relationship to cancer of the lung In 1940 Barksdale[100] expressed concern that while pure food laws permitted only 1 43 parts per million of arsenic tobacco might have fifty times that amount He recognized that the arsenic in all American tobacco was due to the use of insecticides and contrived a mechanical smoker to collect the arsenic for assay He found 0 0365 to 0 0495 mg of As in each cigarette By subtracting the arsenic which remained in the ash and in the butt he found values for cigarette smoke of 0 002 to 0 004 mg of As per ten cigarettes Barksdale considered tobacco to be the source of the arsenic in several cases of characteristic arsenical dermatitis of which he gave case histories

In the following year Carratalá and Vucetich[101] reported on the arsenic content of Argentinian tobacco They also recognized that arsenical dusts and sprays used in controlling plant diseases were the source They found from 0 0 to 0 035 mg of arsenic per kg of tobacco This wide variance from the results of Barksdale[100] may have been due to differences in methods of assay or to actual

differences in the tobacco Carratalá and Vucetich found one sixth of the arsenic to be retained in the ash

The earlier literature was reviewed in 1945 by Thomas and Collier[10] who reported their own results with apparatus which simulated the varying air currents of actual smoking Their interest was directed primarily toward the arsenic in the smoke They found that from 11 to 23 per cent of the arsenic in tobacco was contained in the smoke the remainder being distributed between the ash and the butt The concentration of arsenious oxide in puffed smoke ranged from 0 2 to 3 0 mg per cu m with cigars, from 1 7 to 5 7 mg per cu m with pipe tobacco, and from 3 3 to 10 5 mg per cu m with cigarettes

Of the volatilized arsenic in the smoke, some must leave the body by exhalation, as has been recognized by Daff and Kennaway[103] Presumably the amount retained is small In their report of 1950, they gave detailed information on the arsenic content of fifteen brands of cigarettes which was found to range from 0 to 106 μg per gm (μg per gm = parts per million) of As_2O_3 The lowest values were found in nine brands classed as Turkish and in French and Rhodesian tobacco Even with the same brand the amounts in the upper ranges were very variable Relatively high values were found for three American brands, with 25 3 to 47 0 μg per gm of As_2O_3 By subtracting the As content of butt and ash from that of the entire cigarette, it appeared that from 7 6 to 18 2 per cent of the arsenic was 'lost' in smoking

Because there are differences in the arsenic content of tobacco Daff, Doll, and Kennaway[104] attempted a comparison between the types of tobacco smoked and the incidence of cancer of the lung in various countries Their paper of 1951 is a rich collection of data on this and related subjects Information in respect to Turkey seems particularly important Having in mind that Turkish to

acco is low in arsenic and that Turkey produces an ex ss of tobacco so that Turkish tobacco is smoked almost xclusively the high incidence of cancer of the lung reborted from Istanbul

> shows that the arsenic content of tobacco has not provided any simple and exclusive explanation of the association between cigarette smoking and this form of cancer

n the other hand an affirmative argument might be ade for Iceland where the amount of tobacco used as garettes is small and a very low incidence of pulmonary arcinoma is reported (Dungal[105]) Further studies along us line are indicated

Tars from Tobacco The amount and character of the r which is produced when tobacco is burned will de nd upon such physical conditions as the temperature of ombustion the supply of oxygen and the compactness nd dampness of the tobacco Smoking methods are erefore important as is also the opportunity for conden tion and sublimation of volatile products through cool g and filtration In well conducted experiments with moking machines" the apparatus is so contrived as to ve alternating periods of active draft and of no draft as to simulate the conditions of smoking Attention is ven also to the length of the butt when it is discarded nce tars and particulate matter will be retained to some xtent in the unburned portion of a cigarette the more ompletely it is smoked the greater the proportion of ch products which will be inspired There can be no oubt that under suitable conditions of incomplete com istion carcinogenic products are included in the tar and ot from tobacco and also from cigarette paper

McNally[106] in 1932 collected tar from cigarette smoke d determined some of its major constituents This was

done with only slight reference to pulmonary cancer and with greater concern over chronic bronchitis and leukoplakia His animal experiments were not conclusive since most of the animals died too soon to expect the appearance of cancers Of particular interest is the statement that

> cigarettes should not be smoked too short, as the last two centimeters retain most of the tar and other products of incomplete combustion

Bogen and Loomis[107] also failed to produce neoplasms of the skin of mice by the application of tobacco tar, although they were uniformly successful in producing papillomas and finally squamous celled carcinomas of the skin of control mice to which gas house tar was applied Production of cutaneous cancer by tar from burning tobacco has been reported for rabbits by Lamb and Sanders[108] and for mice by Flory,[109] and by Graham Wynder, and Croninger,[110] and others Flory reviewed the work on tobacco tars before 1940 It is of interest that Wacker and Schmincke[111] were injecting pipe tar into rabbits in 1911, [translation] "because carcinoma of the lung occurs in tobacco handlers and cancer of the lip in pipe smokers

There is also an extensive group of reports on the attempted production of pulmonary neoplasms in mice by exposure to tobacco smoke Results have been highly variable Lorenz Stewart Daniel and Nelson[11] exposed strain A mice to tobacco smoke for several hours each day for from 25 to 250 days No increase in lung tumors was observed Stewart[113] has commented recently on these results to the effect that polycyclic hydrocarbons of known carcinogenic activity are not formed in the combustion of tobacco in the presence of oxygen at certain levels His recent comprehensive survey of pulmonary tumors in

animals with particular reference to mice is documented with seventy two references which will make it clear why a complete review of this subject would be out of scale in this discussion However this is an appropriate point at which to comment on mice and other laboratory animals as test objects for suspected pulmonary carcinogens

Difficulty in Determining Pulmonary Carcinogens by Animal Experimentation In view of the comparative ease with which aliphatic and polycyclic hydrocarbons can be tested for carcinogenicity in laboratory animals particularly in mice it may well be asked why there cannot be a direct experimental approach to testing the suspected causes of pulmonary cancer Such attempts have been made but they have not given definite answers as yet

The mouse would seem to be the animal of choice because of the frequency with which pulmonary neoplasms develop apparently spontaneously in that species But this very frequency introduces a statistical hazard It must be shown by a sufficiently large series of animals that the number of neoplasms of the lung developing under experimental conditions is significantly greater than in a control group Here the strain of mice used is of utmost importance Of strain A mice 80 to 90 per cent may develop "spontaneous" pulmonary tumors while strain L mice rarely develop such neoplasms Moreover those strains which have a relatively high incidence of "spontaneous" tumors are precisely the ones which are particularly susceptible to environmental factors (Shimkin[114])

In the second place neither the spontaneously occurring neoplasms nor the induced neoplasms of the lungs of mice bear any close resemblance to bronchogenic cancer of men In mice tumors are usually peripheral and multiple appear to be of bronchiolar or alveolar origin are composed of low columnar or cuboidal cells and

metastasis is rare In its usual forms, bronchogenic carcinoma of man is more or less diametrically opposite for each of the features mentioned

In the third place, it is probably impossible to simulate in the mouse the prolonged "lag" or "latent" period which is so conspicuous in man A mouse at eighteen months may be as old as a man at fifty years as judged by the life pattern of mice That does not mean that there have been as many cycles of cellular replacement in the bronchial tissues of the mouse as of the man There is considerable evidence, which cannot be displayed here that the carcerogenic effect of some extrinsic factors depends upon cell selection applied to many successive generations of cells

These are three important reasons why the problems of causation of cancer of the lung by environmental agents cannot be solved within a few months or, at the most in a few years of animal experimentation

Chronic Inflammatory or Trophic Changes, Non infective and Associated with Smoking "Cigarette Cough" In an earlier section it has been possible to exclude for the greater part infective bronchitis and pneumonitis, and particularly pandemic influenza and the post influenzal complications as causes of the general increase in pulmonary cancer The same cannot be said for those chronic inflammatory, trophic, and metaplastic processes which are known to accompany protracted and more or less heavy smoking In the intensive search for specific carcinogens in tobacco, tobacco tar, and tobacco smoke these more general effects have received *less attention* than they deserve Coughing itself is known to aggravate inflammatory conditions of the bronchial and tracheal mucosa and mucosal glands, and behind the actual mechanism of coughing are those functional and structural al

terations which activate the cough reflex Thus search for specific carcinogens may not give the answer to the increasing incidence of bronchogenic carcinoma It may be found that physical and chemical properties of tobacco smoke which would never be carcinogenic in short term experiments but which induce dryness mild chronic inflammation and metaplasia and which frequently incite coughing are responsible This supposition is in complete accord with what is known about the effect of an extended period of risk and of intensified risk from increased amount of tobacco smoked

Co carcinogenesis In the sense that extrinsic factors act upon tissues possessing an intrinsic facility for reproduction it may be said that all cancer results from co carcinogens More precisely the terms co carcinogenesis and syn carcinogenesis refer to the effective action of two or more extrinsic agents These may be synergistic in that each augments the essential activity of the other or they may be simply additive or more frequently one may produce a preliminary alteration in the cells which makes them vulnerable to a second agent There is both clinical and experimental evidence of co carcinogenesis in a variety of combinations but as yet this principle has not been used effectively in explaining the origin of bronchial carcinoma If no single carcinogen can be proved responsible the possibility of co carcinogenic action must be entertained

The Latent or Lag Period as a Bar to Immediate Determination of the Mode of Action of Cigarette Smoking Throughout this discussion of the causes of primary cancer of the lung reference has been made to the essential element of protracted exposure to risk and also to the fact that cancer may not appear until some years after exposure has ceased This is true of various agents sus

pected of inducing occupational cancer of the lung Table XI is abridged from a more general tabulation by Hueper

As has been demonstrated repeatedly by the tables and graphs which have been presented, the latent period for cigarette smoking is usually not less than ten years and the intensity of the effect increases throughout life For

TABLE XI
LATENT PERIODS OF OCCUPATIONAL CANCER

Organ and Agent	*Average Latent Period*	*Range of Latent Period*
Lung	Years	Years
Asbestos	18	15-21
Chromates	15	5-47
Nickel carbonyl	22	6-30
Tar fumes	16	9-23
Ionizing radiation	25-35	7-50

Abridged from Hueper *Public Health Reports* 67 773-779 1952. Reproduced by permission.

some persons the latent period may appear to be forty or fifty years This shows the frustrating futility of attempting evaluation of varying methods of smoking or of cigarette holders or of filters, by establishing human experimental groups in the way in which most experimental investigations are conducted Even if dependable human subjects were at hand in sufficient numbers, the results might not be known for a generation To some extent the prospective method which starts with the smoking habits of ten or more years ago, avoids this delay, but as yet this has given a definite answer only to the main question

Lung Cancer Among Non smokers

Primary pulmonary cancer occurs among those who are classed as non smokers The definition of a non smoker has not been uniform If it is taken to mean a person who

has never smoked one cigarette one pipeful of tobacco or one cigar in his lifetime practically all males and most females would be excluded Doll and Hill[96] considered a practical definition of a non smoker to be

> a person who has never consistently smoked for as long as one year at the rate of as much as one cigarette or one gramme of tobacco a day

The effect on a non smoker of exposure to the tobacco smoke of others has, as yet received very little serious consideration Statistical investigation will encounter many difficulties Some years ago the rhetorical question was posed by Lickint[116] whether the non smoking wife who had lived many years with a heavy smoker was still a non smoker for both clinical and statistical purposes At the symposium on the endemiology of cancer of the lung at Louvain in 1952 the following dialogue[117] occurred

> *Dr Hammond* Are you suggesting that the control group should never have been exposed to tobacco smoke?
> *Dr Maisin* This would not be possible in a civilized community I have never smoked but look how I am exposed to tobacco smoke just now

When detailed answers are known the passive exposure of the non smoker may be found to be at least a co factor in the production of bronchogenic carcinoma but any suggestion now to that effect is highly speculative

Using the definition of a non smoker previously cited from Doll and Hill[96] Doll[118] attempted a statistical investigation of cancer of the lung in non smokers The difficulties in such a project are obvious in view of the proportionately small class of non smokers and the extremely small class of non smokers with cancer of the lung The author commented on the "bold assumptions" which were necessary and suggested that the incidence

of lung cancer in non smokers may be the same in men and in women, and in residents in areas of differing density of population Environmental factors other than those per taining to smoking should bear upon non smokers and smokers alike Doll concluded, further, that one in five of lung cancer deaths in persons aged twenty five to seventy four years in 1950, may be attributable to causes other than those associated with smoking

Comparative Risk of Developing Cancer of the Lung for Smokers and Non smokers

Under the appropriate topic I have included reference to the work of Cutler and Loveland[17] who found that of 1,000 white males born in 1910 and still living in 1950 43 may be expected to have developed cancer of the lung by age eighty How will this incidence be apportioned between smokers and non smokers? As Cutler and Love land pointed out if the risk of developing cancer of the lung were 1 in 100 000 for non smokers and 1 in 10,000 for smokers, the entire question might be regarded as trivial However, when the sum of these risks must ap proximate 43 in 1 000 determination of whatever differ ence may exist becomes very important By an extension of the method used by Cornfield,[119] and with his assist ance Cutler and Loveland have developed an answer which is embodied in Table XII The data on smokers and non smokers were obtained from three comparative studies to which reference has been made previously These were the work of Sadowsky, Gilliam and Corn field,[1 9] of Wynder and Graham,[95] and of Doll and Hill[96] Together, they provided information on 2 434 cases of can cer of the lung and 2 729 non cancerous controls When separately analyzed the three studies were in agreement as to general trends but differed somewhat in the predicted number of cases in the non smokers Two assumptions

were necessary to complete the analysis. One was that the control group was representative of the smoking characteristics of the general population from which the lung cancer patients were derived. The other had to do with establishing cigarette equivalents for cigars and pipe smoking. Neither assumption would appear to result in more than minor alteration in the number of cases predicted even if it were not entirely correct.

TABLE VII
CASES OF LUNG CANCER EXPECTED TO DEVELOP PER 1000
WHITE MALES 40 YEARS OF AGE

Smoking Class	*By Age 80*	*By Age 70*	*By Age 60*
Non smokers	6	4	2
Smokers, daily of			
½ pack or less	25	16	6
½ to 1 pack	49	30	11
More than 1 pack	80	53	23
All persons	43	27	11

(After Cutler and Loveland[7])

The results of this investigation not only showed that in the respective age groups the liability to lung cancer of smokers in general was from four and one half to six times that of non smokers but it indicated very clearly the effect of amount and of duration of smoking. The added years at risk are very important and the effect is cumulative even in the eighth decade of life. This is the answer to the fatalistic attitude that any carcinogenic effect has been exerted in the first decade or two of smoking.

BRONCHOGENIC CARCINOMA AT THE MID-CENTURY STATISTICALLY ESTABLISHED ASSOCIATIONS

Apart from the greater liability to bronchogenic cancer in certain occupational groups which accounts for but a small part of the total incidence strong statistical evidence has been presented for association between certain

human attributes and primary cancer of the lung These attributes are maleness, urban living industrialization and the smoking of tobacco, particularly as cigarettes

Maleness Maleness is a biologic quality, presumably has not changed in the last half century Yet the proportion of males developing cancer of the lung has increased faster than the proportion of females developing cancer of the lung although both are increasing This alone establishes that there must be an extrinsic agent If maleness is significant it must be as a co carcinogen In 1929, I wrote with complete confidence that if smoking was a cause of bronchogenic carcinoma there would be a trend toward sex equality in incidence in another generation As yet such equality has not developed In fact the gap has widened However more is known now about the importance of the latent period and of prolonged years of risk than in 1929 It is still evident that a much greater proportion of males have been heavy smokers for twenty or more years than of females As appears in Table VIII Doll and Hill[96] found only 14 women who smoked more than 25 cigarettes a day in the combined cancerous and control groups, which totalled 216 If the smoking habits of the women had been like those of the 2,714 men 40 would have been expected In other words, the apparent effect of maleness cannot be separated even today from the presumptive effect of smoking

Urban living and industrialization include the concentration of motor vehicles and of increased sources of air pollution The many carcinogenic possibilities therein cannot be cast aside completely Some of the known carcinogens, even in minute amounts are potent producers of malignant neoplasms elsewhere than in the lungs There is evidence for carcinogens not yet identified in the products of incomplete oxidation as found in the exhaust of internal combustion engines It is an arresting fact that

arguments for the importance of tobacco which are based on economic data such as increasing national consumption apply almost equally well to the automobile But it is true also that the manner and degree of use of tobacco vary between urban and rural living and that long term

Smoking and Pulmonary Cancer
Association Proved—Causal Relation Presumptive
If Causal

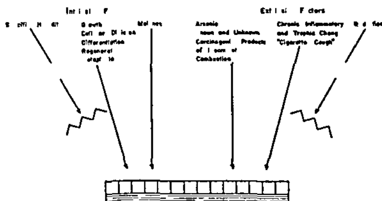


FIGURE 20 If the association between smoking and pulmonary cancer should prove to be causal the relationship of intrinsic and extrinsic factors might prove to be that which is shown in this schematic diagram Symbols have the same significance as in Figures 13 and 19

excessive cigarette smokers are in proportionately greater numbers in larger communities Tobacco chewing and pipe smoking in the villages and on the farm have not been replaced by cigarette smoking as they have in the city It is conceivable that the association with urban living and industrialization may be resolved on the basis of cigarette smoking although evidence on that score falls short of proof

Smoking of tobacco particularly the excessive smoking

of cigarettes over a long period, is associated definitely with the occurrence of bronchogenic carcinoma according to the results of several different methods of statistical investigation Association does not necessarily imply a causal relation, but there has been no other satisfactory explanation why this association should prevail Non smokers develop pulmonary cancer and many heavy smokers escape pulmonary cancer, but for a long term heavy smoker the chance that he will develop cancer of the lung by age eighty is of the general order of fifteen times greater than for a non smoker (Cutler and Loveland[17]) In about four fifths of the cases of primary cancer of the lung association with tobacco smoking appears to be a significant factor (Doll[118])

If the association between tobacco smoking and bronchogenic cancer is accepted as of causal significance what the specific cause may be remains unknown Arsenic the known and unknown carcinogens resulting from incomplete combustion of organic matter, and the complex of factors which produce those dystrophic changes which may find expression in cigarette cough" are the chief suspects One of these may act alone or with others through a relationship of co carcinogenesis or of syn carcinogenesis We can look to the future with assurance that, if the relationship is causal, the nature of the causal agent eventually will be determined Its identification or perchance the discovery of new evidence which will point the finger of suspicion away from smoking is a challenging possibility for each and every physician The solution may come through a combination of the prospective statistical method and intensive case studies With such knowledge prevention of four fifths or more of the present mortality from bronchogenic carcinoma would be a reasonable expectation

VI

EPICRISIS

In this discussion of the historical and practical approaches to the causes of primary cancer of the lung I have made every effort to give as complete and fair a presentation of the evidence as the scale of treatment made possible I have endeavored to present the evidence in an unbiased manner so that each reader could form his own conclusions as the evidence unfolded I have not been an advocate for any particular view and certainly I have no intention of being a crusader

My own views have undergone change through the years I early subscribed to the then prevailing opinion that protoplasm was relatively stable and the chromosomes particularly so The rate of incidence of cancer in any organ was considered to be a fairly constant function not readily influenced by environment although numerous occupational carcinomas of the skin had been demonstrated At first it seemed improbable to me that the increase in cancer of the lung was something new and I joined others in attempting to explain it by the aging population by the advent of radiography by clinical awareness and by better diagnostic methods in general These explanations eventually proved inadequate and it was necessary to admit that some recently acquired feature of our way of life was very rapidly changing the incidence of pulmonary cancer

Similarly, I have been resistant to a ready acceptance of the association between cigarette smoking and bronchogenic carcinoma I have searched the literature for other

reasonable explanations or for recognizable fallacies I have found none of importance As of today, I must agree with many of the specialists in statistical analysis and in the endemiology of cancer, that this association has been established

What is the next step? When will it be not only proper but requisite that the medical profession take cognizance? Those are questions which I cannot and should not attempt to answer at the moment I can however, give you the answer of J H Maisin and J Clemmesen, who were editors'[1] for the report of the Louvain Symposium on the Endemiology of Cancer of the Lung In the final paragraphs of their editorial they commented that it was about 150 years after Percivall Pott explained the etiology of chimney sweeps cancer and prescribed methods for its prevention before carcinogens were demonstrated in soot and continued

> May we show the same practical sense as our forefathers and not look for direct proofs which are out of reach before we transmit experience into practical measures

VII

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This Book

CAUSAL FACTORS IN CANCER OF THE LUNG

By
CARL V WELLER, M S, M D

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